Pathophysiology of Migraine –

A disorder of sensory processing

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Running title- Migraine pathophysiology

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Abstract

Plaguing humans for more than two millennia, manifest on every continent studied, and with more than one billion patients having at attack in any year, migraine stands as the sixth most common cause of disability on the planet. The pathophysiology of migraine has emerged from a historical consideration of the “humors” through mid-twentieth century distraction of the now defunct Vascular Theory to a clear place as a neurologic disorder. It could be said there are three questions: why, how and when? Why: migraine is largely accepted to be an inherited tendency for the brain to lose control of its inputs. How: the now classical afferent trigeminal durovascular afferent pathway has been explored in laboratory and clinic; interrogated with immunohistochemistry to functional brain imaging to offer a roadmap of the attack. When: migraine attacks emerge due to a disorder of brain sensory processing that itself likely cycles, influenced by genetics and the environment. In the first, premonitory, phase that precedes headache; brainstem and diencephalic systems modulating afferent signals, light- photophobia or sound- phonophobia; begin to dysfunction and eventually to evolve to the pain phase and with time the resolution or postdromal phase. Understanding the biology of migraine through careful bench-based research has led to major classes of therapeutics being identified: triptans- serotonin 5-$HT_{1B/1D}$ receptor agonists, gepants- calcitonin gene-related peptide- CGRP receptor antagonists, ditans, 5-HT_{1F} receptor agonists, CGRP mechanisms monoclonal antibodies and glurants- $mGlu_5$ modulators; with the promise of more to come. Investment in understanding migraine has been very successful and leaves us at a new dawn, able to transform its impact on a global scale, as well as understand fundamental aspects of human biology.

I. Introduction

Migraine is a severe and disabling brain condition (340), listed as the 6th most disabling disorder globally by the World Health Organization; and the most disabling of all neurological disorders (303). Unfortunately its ranking is increasing with time (620, 827). It has a one year prevalence of 15-18% worldwide (536, 539), if both episodic and chronic migraine are included, and has a huge financial burden on global economies; costing the US $US19.6 (757) and the European Union €27 billion (43) annually. It is likely that the true socio-economic cost of migraine is currently significantly higher given a recent study highlighting nearly £6 billion in service use and lost employment in the UK alone (591). Migraine predominantly affects females, 3:1, and significantly affects quality of life (137), in many cases during peak years of productivity. It is characterized by attacks of unilateral, throbbing head pain, with sensitivity to movement, visual, auditory and other afferents inputs (386). Other symptoms such as tiredness, irritability, reduced concentration and yawning can precede the headache by up to 48 hours (300): the premonitory phase. Most attacks are followed by hours or a day of feeling unwell, usually with tiredness called the postdrome (299, 465). Additionally in approximately one-third of migraine patients their attacks are associated by neurological deficits associated which include cortical perturbations, collectively termed migraine aura (678).

A. Historical Aspects

Headache has been known for probably 6000 years ago, although it is not clear what type of headache (232). Migraine, indeed the more modern construct of chronic migraine, can be readily recognized in the work of Willis in the Seventeenth Century (855). The debate over the pathophysiology of migraine has largely centered on neural or vascular mechanisms that may be involved in triggering and driving attacks. The arguments have existed for several centuries and have cycled somewhat. Historically, nearly 150 years ago both seemed to be prevalent, migraine was thought of as a disorder of the brain by Edward Liveing. In his famous text *'On Megrim, Sick Headache, and some allied disorders: a contribution to the pathology of nerve-storms'*, he describes migraine as the result of 'nerve-storm, an inherited tendency for the discharge of nerve force, a 'neurosal seizure'' (544). At the same time Peter Wallwork Latham lectured (509, 510) and published *'On Nervous or Sick-Headache'* (511), describing the likely origin of migraine through vasodilation, triggered, interestingly, by aura; both theories have been reviewed in historical context (840). Latham used experimental observations in his laboratory, and migraine triggers, to demonstrate his theory, and he could be considered a trailblazer in some ways.

The studies of Wolff and colleagues in the 1940s on cranial blood vessels in conscious patients revisited the idea of migraine perhaps most likely being a vascular disorder (358, 679, 861). The concept persisted for nearly five decades until the development of sumatriptan both supported it (266), and yet led to its further questioning (435). As it emerged sumatriptan had both vascular and neural effects, so the role of the cranial vasculature was questioned. The theory of migraine pain being due to a sterile inflammation of the dural meninges caused by antidromic

activation of the trigeminal nerve evolved (566). However, the spectacular failure of as many as ten compounds that were active in the preclinical dural neurogenic inflammation model has caste consider doubt on the concept (660). The description of purely neural effects of sumatriptan, such as those on nociceptive durovascular neurons in the trigeminocervical complex (419, 462) began a renaissance of thinking of migraine and its treatment as primarily a neural construct.

B. Where we do stand now?

Migraine certainly involves the brain: in some respects the controversy remains rather similar and pivots around two issues: initiation and the origin of the pain. While the initiation of a migraine attack is frequently associated with reported internal and external triggers, even this concept is being revisited by a more central interpretation that arises when considering the premonitory phase. The origin of the neuronal mechanisms that underlie the primary condition in susceptible people are still not known, and that must be a primary goal of research in this area. It is certainly widely accepted that migraine involves activation and sensitization of trigeminovascular pathways, as well as brainstem and diencephalic nuclei (21, 91). Furthermore a primary dysregulation of sensory processing is likely to result in the constellation of neurological symptoms that affect our senses. It has been suggested that migraine may be considered as a brain state of altered excitability (158, 182, 183, 206, 750). Certainly migrainous premonitory symptoms can occur many days before the headache (300, 466, 712); they are neurological symptoms that are non-nociceptive in their nature, which points to an origin in the brain. Furthermore the identification of multiple genes responsible for familial hemiplegic

migraine (FHM) (268), which increases the likelihood of severe aura symptoms, and the identification of a genetic predisposition in family studies (795), provides strong support for the view that migraineurs may be genetically susceptible or predisposed. While the term excitability is often used to characterize these responses, a state of hypersynchrony (49, 627) would explain the clinical symptoms of migraine very well.

C. Objectives of the review

The objective of this review is to describe the clinical manifestations of migraine in a context of the clinical and preclinical data that illustrate the anatomy, physiology and pharmacology relevant to these symptoms. The reviewed data will support the theory that migraine, at its core, is a disorder of the brain, caused by a dysfunction in areas of the brainstem and diencephalon that alter the perception of sensory inputs, and cause other neurological deficits. We will show how brain function is broadly affected when these systems changes take place in migraine.

II. Clinical Manifestations

Migraine is a complex and multifaceted disorder of the brain which in its entirety may last over several days. Migraine has been classically dissected into four phases: the premonitory, aura, headache and the postdrome phase. These may occur in a linear sequential order but in most cases migraine phases show a significant overlap, such that the linear ordering is both attractive and deceptive in its simplicity. While we will try to dissect the pathophysiology of the symptomatology in stages, it is important to recognize that some symptoms, such as tiredness

or concentration impairment, may well attend all phases. In reality, only head pain, by its absence or presence, marks itself out.

A. International Classification of Headache Disorders (ICHD)

The International Classification of Headache Disorders (ICHD), a valuable tool for the standardized diagnosis of primary and secondary headache disorders, which is now available in its third edition (ICHD-3, summarized in Table 1) (386). From its first (384) through second (385) editions, it led to a significant improvement in diagnostic accuracy, and to improved and focused preclinical and clinical research, in particular clinical trials, in an unprecedented way. However, given its aim to define the clinical picture for the use in a clinical setting, it focuses on the headache and aura phases as they are characterized by disabling symptoms that commonly require medical intervention. Its weakness is the over-reliance on a polythetic approach where there are a broad set of criteria without one or other being necessary or sufficient. This contrasts to a monothetic approach where some or all parts are necessary and sufficient. The conflict comes with face validity for clinicians; it remains an unresolved issue. The impact on physiology is where migraine symptoms, such as osmophobia (464, 714, 878), are not mentioned because they are not usually “needed” by a polythetic approach, which may leave them less studied. In the review, we aim to capture as much of the pathophysiology as possible, and will be inclusive where possible, symptom-wise, and use the concept of phases, as limited as they be in a disorder that often is marked by a continuum.

B. Premonitory Symptoms

The majority of migraineurs experience a range of premonitory symptoms well before the typical migraine headache initiates. Despite being described in the literature for decades (228) their pathophysiological relevance and their clinical implications have been largely neglected. Premonitory symptoms of a migraine attack, which may precede the headache phase by up to 72 hours (300), include changes in mood and activity, irritability, fatigue, food cravings, repetitive yawning, stiff neck, and phonophobia. These symptoms may endure well into the aura, headache (373) and even postdrome phases (105, 299, 465). The current ICHD-3beta precludes the existence of premonitory symptoms within two hours of headache onset (386); this clearly has no logical basis and needs attention. We adopted above the definition of the symptoms starting anytime prior to headache. The consistency of these symptoms allows some migraineurs to reliably predict their migraine attacks (300). The fact that these symptoms are to a large extent of hypothalamic origin and imaging studies using H_2O PET show an increase in hypothalamic blood flow during the presence of premonitory symptoms (559), suggests a prominent role of the hypothalamus in the early stages of the attack.

Interestingly many of the trigger factors described by migraineurs, such as for example sleep deprivation, hunger or bright light may in fact represent premonitory symptoms of an already ongoing attack. This relationship explains why observations in clinical studies that aimed at prospectively identifying and validating trigger factors of migraine commonly differ from findings obtained from questionnaire-based studies in which patients merely describe their own perception of factors triggering their migraine attacks (401).

Understanding the pathophysiological mechanisms underlying the premonitory symptoms may offer insights in the structures of the central nervous system involved in the early phases of a migraine attack and ultimately contribute to identifying a novel therapeutic approach that would exert its action before the headache begins.

C. Aura phase

About a third of migraineurs experience transient neurological deficits, the migraine aura, in the context of their migraine attacks (678). The ICHD-3 defines the migraine aura as one or more transient, fully reversible neurological deficits, of which at least one has to have a unilateral localization, that develop over five or more minutes and of which each deficit lasts between 5 and 60 minutes. Detailed prospective diary study work has shown that 26 % of patients have at least one of three auras that lasts longer than an hour (825). This draws attention to the polythetic problem, since investigation of aura lasting over an hour would be a large waste of resources. Five per cent of auras are over four hours (825); so perhaps that is a useful cut-off. While a visual aura, which may show positive (fortification spectra), negative (scotoma) or both phenomena is found in over 90 % of the cases, and the most common deficit, sensory, motor, speech, brainstem and retinal aura symptoms may also occur. Aura symptoms may precede the headache phase but may last well into the headache phase or even initiate during the headache phase. In contrast to the common belief that the aura and headache phases follow a sequential order, recent studies have demonstrated that the overlap of these phases is very common rather than being the exception (373). In migraineurs suffering from

motor aura symptoms such as in hemiplegic migraine, aura symptoms usually show a longer duration and may last up to 72 hours. In these severe cases of migraine aura, the deficits usually coexist with migraine headache. Remarkably, positive phenomena in hemiplegic aura are very unusual; one would predict jerks prior to weakness if there was invariably an initial depolarization. Since that is not the rule, the clinical phenomenology insists that one keeps an open mind about migraine aura pathophysiology going forward.

A transient wave of neuronal depolarization of the cortex, the cortical spreading depression (CSD), is believed to be the pathophysiological brain mechanism underlying the clinical phenomenon of migraine aura. While in humans the electrophysiological correlate of a CSD has not been demonstrated during a migraine aura, the correlation between the neurophysiological characteristics of a CSD, its retinotopic propagation on the visual cortex and the characteristics and dynamics of the visual deficits suggest CSD as its pathophysiological correlate (158, 513). Indirect observations derived from imaging studies further support this concept (192, 366, 640). Whether CSD is causally linked to the initiation of headache is still extensively debated and discussed in greater detail in below, nevertheless, based on the current understanding of migraine, it is unlikely that CSD is involved in the initiation of the complete syndrome of migraine (307).

D. Headache Phase

In the latest edition of the ICHD-3, migraine is defined as headache attacks lasting 4-72 hours that are accompanied by nausea, photophobia and phonophobia, or both. The headache is

characterized as unilateral, pulsating, of moderate or severe intensity and aggravated by physical activity; two of these characteristics suffice to fulfill the diagnostic criteria. In comparison to previous editions, ICHD-3 distinguishes chronic migraine, which occurs on 15 or more days per month, from episodic migraine in a more practical fashion, building on the appendix definition (637). Whether the distinction has utility as it stands, ie whether the fifteen day cut-off is appropriate, remains unclear. As yet the distinction has not offered ground-breaking physiological insights.

E. Postdrome

The postdrome phase has been largely neglected and is not even defined in the glossary of terms in ICHD-3beta (386). The findings from the few studies that have focused on this last phase of a migraine attack indicate that its characteristic symptoms reflect those observed during the premonitory phase (105, 299, 465). A prospective, systematic electronic diary study, typical postdrome symptoms include tiredness, difficulties in concentrating and neck stiffness. It remains unclear whether these symptoms initiate in the premonitory phase and persist throughout the headache phase into the postdrome phase, if they may also initiate during the headache phase, or even appear after the headache phase has ended. Migraineurs commonly relate symptoms of the postdrome phase to the medication that successfully abolished their headache indicating that these symptoms appear or re-appear after the headache phase has ended while they seem to play a negligible role during the headache phase. However, a meta-analysis of a clinical trial program revealed that postdrome symptoms are seen in the placebo arm most prominently when pain is relieved (318).

III. Imaging migraine pathophysiology

The phases of migraine, including the inter-attack phase, which are described above clinically present a useful way to consider brain imaging results. Given the basic concept that migraine is inherited- a trait, which is well illustrated in electrophysiological studies (206, 709), we shall cover those studies in brief as a backdrop before discussing imaging findings. All these methods suffer to some extent from the principle issue of trait and state. This is true of functional inter-ictal studies as there is no external validation that nothing has started or that the attack has ended. It can be argued that triggered studies have the advantaged of homogeneity relative to when the migraine attack process commenced. Another overall issue that applies to all physiological studies in migraine; indeed all studies where controls are used is how one factors in false negative history in controls. The cumulative lifetime incidence of episodic migraine in North American females is 43% (759). If one considers probable migraine and chronic migraine, and the vigorous debate around over-lap with tension-type headache, being sure a control does not harbor migraine biology is very challenging. The authors find in any study they have done finding “vanilla” controls is the most difficult part of the work. These caveats apply across all these modalities.

A. Neurophysiology of migraine as a backdrop to imaging

The application of neurophysiological methods in migraine patients has offered important insights into the condition. These approaches offer temporal over spatial discrimination and

prior to MRI, and still to some extent, better opportunities for repetition. What has emerged very clearly from studies in visual, somatosensory, auditory and nociceptive domains is activation that differs from controls reliably. A prevailing synthesis of the data is to consider thalamocortical dysrhythmia (185, 819) to be key to migraine pathophysiology (206). It has been observed for some time that migraine patients fail to habituate normally between attacks, for example the intensity dependence auditory evoked potentials is augmented between attacks in migraine patients (37, 834). Remarkably this normalizes in the days before an attack (452). Interestingly this measure has a serotonin dependence that can be altered by triptans, serotonin 5-$HT_{1B/1D}$ receptor agonists (See Section IX) (671). Potentiation of the passive "oddball" auditory event-related potential similarly suggests migraineur's brains do not habituate in non-migraineurs do (833), as does an interical habituation deficit as measured by the nociceptive blink reflex in migraineurs (213). This has led to the concept that the migraine brain over-responds, as distinct from being hyperexcitable (38, 181, 182, 709)

B. Inter-attack imaging studies

1. Structural studies

Several studies have identified differences between migraineurs and control subjects in respect of brain structure. Structural studies are typically cross-sectional, and have to be interpreted in view of functional interactions of pain processing areas with the trigeminal system. Voxel-based morphometry has demonstrated reduced gray matter in pain processing areas, such as the anterior cingulate cortex, amygdala, insula, operculum, and the frontal, temporal and precentral gyri. Interestingly, gray matter reduction in the anterior cingulate cortex was

correlated with the frequency of migraine attacks (812). In contrast, gray matter volume was increased in the caudate nuclei bilaterally in migraineurs with high frequency attacks if compared to patients with low frequency (555). The somatosensory cortex, and especially the somatotopical representation of head and face further depicted increased thickness in comparison to controls (199). The same group used diffusion tensor imaging to evaluate white matter integrity. They demonstrated reduced fractional anisotropy in migraineurs along the thalamocortical tract, in migraineurs with aura also in the ventral trigeminothalamic tract, and in migraineurs without aura in the ventrolateral periaqueductal gray (PAG) (199). In another study, diffusion tensor imaging was applied to 16 patients and 15 controls to measure the extent of tissue damage in the brain. Only minor diffusivity changes were identified in the gray matter whereas the normal-appearing white matter and changes in brain volume were equally distributed in both groups (689). In a larger study with 22 patients and 20 controls, T1 relaxation time was shorter in the thalamus of migraine with aura patients compared with migraine without aura and healthy controls. (359). In an international collaboration 3T scans from 131 migraineurs were obtained and pooled and showed volume loss in patients compared to controls in the central nuclear complex, anterior nucleus and lateral dorsal nucleus, as well as reduced striatal volume (553). Overall, the studies demonstrate that the ability of developing migraine attacks is reflected by structural alterations in pain processing areas such as the anterior cingulate cortex and the trigeminal somatosensory system. From the nature of the method, it remains unclear if these changes are the consequence of repetitive migraine attacks or if they are involved in migraine pathophysiology. Using diffusion tensor MRI it was shown that fractional anisotropy was higher and mean diffusivity lower in migraine without aura

patients compared to controls in their thalami between attacks. This change normalized in migraineurs during attacks (184). Importantly, there was correlation between changes in the right thalamus and the days from the last attack (184). Building on these observations using voxel-based morphometry with T1-eeighted 3T MRI it was shown that migraine without aura patients have lower gray matter density in the right inferior parietal lobule, right temporal inferior gyrus, right superior temporal gyrus, and left temporal pole interictally, with no reductions ictally (180). Taken together the data suggest plastic changes attendant the migraine attack that may underlie disorder progression.

2. *Functional studies*

Functional studies complement structural brain imaging. They are typically divided into those looking at the function of the migrainous brain at rest, i.e. the true inter-ictal state, and in those investigating its *response* to external stimuli.

i. Metabolism and Receptor Pharmacology

The classic way of analyzing functional differences between two groups at rest is to assess regional brain metabolism with ^{18}F-FDG PET. This identifies functional differences in migraineurs *independently* from specific external stimuli, as with BOLD-fMRI, or from pre-defined brain areas, as with seed-based 'resting state' analysis. Therefore, studies using ^{18}F-FDG PET can be regarded as very close to the biology of the disease, although exposure to radiation and poor spatio-temporal resolution are clearly limiting factors. Kim and colleagues (467)

compared twenty interictal episodic migraineurs with control subjects. Migraine was associated with hypometabolism of central pain processing areas including bilateral insula, bilateral anterior and posterior cingulate cortex, left premotor and prefrontal cortex, and left primary somatosensory cortex. This suggests a dysfunction of central pain processing in the interictal state possibly reflecting the readiness of the brain to develop migraine attacks. Interestingly, there was no area of hypermetabolism.

ii. Stimulated blood flow changes

Photophobia is one of the key non-head pain symptoms defining migraine (386). Patients typically describe light being too bright (abnormal sensitivity to light) or even painful by causing or worsening head or eye pain (phototic allodynia). Even interictally migraineurs tolerate less luminence than healthy controls (817). Similarly, migraineurs but not controls activate the visual cortex (cuneus and lingual gyrus) when exposed to different luminous intensities as shown in seven interictal migraineurs with $H_2{}^{15}O$-PET (116). Interestingly, the application of trigeminal pain also led to an activation in the same areas in control subjects. This indicates that activation of the trigeminal system, as might happen during migraine attacks, could result in a facilitation of the retino-geniculate-cortical pathway of visual processing and/or a dysfunction of visual association areas causing photophobia.

Using fMRI, Moulton and colleagues (614) measured the brainstem response to heat stimuli and identified a reduced response in the nucleus cuneiformis, which is known to be a

component of brainstem pain modulating circuits. During migraine attacks, this dysfunction might lead to hyperexcitability of trigeminovascular neurons and thus to the perception of headache. The same group further found the anterior temporal pole of migraineurs being more active after painful heat stimulation when compared to control subjects (613). The temporal pole further depicted increased functional connectivity to various brain regions that might be involved in migrainous symptoms, such as the anterior cingulate cortex, the somatosensory cortex, amygdala, and others. Similarly, it can be shown by investigating the response to painful heat stimulation to the dorsum of the hand that migraineurs with high frequency attacks had reduced BOLD-response in the basal ganglia, putamen, caudate and pallidum, compared to controls (555).

Demarquay and colleagues (207) evaluated olfactory processing in migraineurs with habitual olfactory hypersensitivity. They assessed regional cerebral blood flow (rCBF) in 11 migraineurs and 12 controls. During odor-stimulation migraineurs had increased rCBF in the left temporal pole and lower values in the frontal and temporo-parietal regions, posterior cingulate gyrus and right locus coeruleus. Subjects with olfactory hypersensitivity differed from those without in the left piriform cortex and antero-superior temporal gyrus. Some specific symptoms in migraineurs, such as olfactory hypersensitivity, are therefore associated with a unique cortical response even outside of attacks. Taken together, these data suggest that various cortical and subcortical areas in the brain of migraineurs respond differently to external stimuli when compared to healthy controls. This might imply that a migraineur's brain is 'dys-excitable' (750)

with pre-conditioned functional abnormalities that concertedly exacerbate during migraine attacks.

iii. Resting-State Studies

While structural brain imaging identifies differences between grey or white matter and stimulus-driven fMRI locates individual dysfunctional areas, the 'resting state' approach assesses the cross-talk between different areas (functional connections) by measuring the correlation of low-frequency spontaneous fluctuations between remote brain areas (280, 281).

Mainero and colleagues demonstrated that migraineurs have stronger connectivity between the PAG and several brain areas that are relevant for nociceptive and somatosensory processing. They further showed an association between this connectivity and frequency of migraine suggesting some pathophysiological relevance of this correlation for pain modulation in migraine (554). Cutaneous allodynia is thought to be the manifestation of central sensitization during migraine attacks. Comparing the 'resting state' connectivity of migraineurs with and without cutaneous allodynia, differences in the connectivity of the PAG/nucleus cuneiformis to various discriminative pain processing centers (brainstem, thalamus, insula, cerebellum) and higher order pain modulating areas (frontal and temporal regions) were identified (719). This implies that individual symptoms during migraine attacks are reflected by interictal abnormal communication between pain-modulating areas. Further, although both groups were migraineurs (386) with normal routine investigations, the presence of ictal

allodynia seems to determine different sub-syndromes of migraine indicating that migraine itself might also be pathophysiologically diverse. Linking studies in the headache phase, seed-based resting state fMRI has demonstrated increased connectivity between primary visual and auditory cortices and the right dorsal anterior insula, and between the dorsal pons and the bilateral anterior insulae; neither correlated with migraine frequency (801), suggesting the changes were a trait of migraine pathophysiology. Another intriguing possibility if fMRI for classification. Using a seed-based approach, resting functional connectivity of the right middle temporal, posterior insula, middle cingulate, left ventromedial prefrontal and bilateral amygdala regions best discriminates migraine and control brains (166). While have a circularity because the gold-standard remains clinical, it can be seen such approaches may yield both insights into biology and *NextGen* approaches to treatment trial outcomes as a biomarker of change, for example in preventive studies.

In contrast to the seed-based resting-state networks, i.e. those identified by looking for the connectivity of one or other 'seed' area (e.g. PAG or nucleus cuneiformis), task-free resting state studies using independent component analysis without *a priori* hypothesis have been conducted. Tessidore and colleagues (788) compared this default mode network of 20 patients with migraine without aura to 20 age- and gender matched controls. Migraineurs had decreased connectivity in prefrontal and temporal regions of the default mode network. The authors speculate that such dysfunction of the default mode network might be related to maladaptive reactions to stress or environment putatively being characteristic for migraine.

In summary, being a migraineur means having subtle differences in brain structure and function even outside of attacks. Importantly, most areas are part of the unspecific pain processing areas or of the trigeminal system. A major challenge is to understand how these differences predispose to migraine attacks, or in other words, which structures drive the 'migraine cycle' from interictal via premonitory phase to the headache phase and, finally, the postdrome period that then runs over back to the interictal phase.

iv. Mitochondrial Energy Metabolism

The recognition of migraine as a component of mitochondrial cytopathies (221) offers an avenue to explore how that biology may produce migraine. An initial study of mitochondrial DNA did not find any of the typical MELAS or MERRF mutations (470). The successful completion of a randomized controlled trial of riboflavin (vitamin B2) as a preventive treatment of migraine (710), further lends an argument to pursue metabolic dysfunction as a possible susceptibility in some patients. Using ^{31}P-NMR spectroscopy Welch and colleagues (843) showed a change in phosphate metabolism in patients with migraine with aura during an attack. Again with ^{31}P-NMR spectroscopy a later study in patients with migraine without aura showed changes in phosphate metabolism (607). Similar results were seen in children (545). Using a 3T MRI and ^{31}P-NMR spectroscopy it has been shown in the occipital cortex of patients with migraine without aura that there are changes in energy metabolism (683). There is, as could be expected some distribution of the energy changes across the patients studied, so it seems likely that these findings could explain some, and not all, of the biology of migraine expression.

C. Premonitory phase

From a clinical perspective, the premonitory phase that connects the asymptomatic interictal phase with the headache attack has to be crucial for understanding the mechanism of migraine ignition. One of the most important fMRI studies in this respect assessed the (de-)activation pattern elicited by trigemino-nociceptive stimulation of the nasal mucosa as the headache day approached (749). When compared to control subjects, interictal migraineurs have reduced activation of the spinal trigeminal nuclei. This deactivation had a cyclic behavior over the course of a migraine interval: there was normalization prior to the next attack and a significant reduction of deactivation during the attack (Figure 1). This cyclic behavior might thus reflect the increased susceptibility of the brain to generate the next attack, and the identification of its pacemaker would be crucial for our understanding of the start of a migraine attack.

The earliest clinical signs of a migraine attack are so-called premonitory symptoms, which occur prior to head pain but already tell the patient that a headache is on its way. Based on their manifestation, they are likely related to the hypothalamus (56, 482) and include concentration problems, tiredness, irritability or depression. When compared to the headache phase, they typically resemble some of the non-headache symptoms of a migraine attack and thus might persist during the headache phase. Recently Maniyar and colleagues (559) triggered migraine attacks in eight patients with migraine without aura in patient who could predict the occurrence of headache by a pronounced premonitory phase. During the premonitory phase, i.e. still in the absence of head pain, $H_2{}^{15}O$-PET demonstrated activation of the hypothalamus,

the midbrain ventral tegmental area, and the PAG (Figure 2). This functional correlate of premonitory symptoms suggests a possible role of the hypothalamus in generating migraine attacks. Of great interest in this regard are data from a single patient whose responses to trigeminal nociceptive stimuli were tracked with BOLD-fMRI over a 30 day period. Hypothalamic responses were increased as the attack neared, and there was coupling of the effects with the dorsolateral pons (715). In addition, the hypothalamus might be important for the non-headache symptoms during the pain phase since when studied in seven spontaneous migraine attacks with $H_2{}^{15}O$- PET activation of the hypothalamus was seen (209) – although the location of both activations were distinct. It is noteworthy that activations seen in the trigeminal-autonomic cephalalgias (575, 576, 581, 582, 748) are more posterior than reported in migraine.

D. Aura phase

The typical visual aura usually begins prior to the headache phase, but can also occur at the same time or even independently from any headaches (373, 825). It often starts with a blind or scintillating spot in the center of the visual field (15). Lashley (506) reported some observations of his own visual aura: in his case, the scotoma increased in size over about one hour drifting in a C-shape toward the temporal field of one side. The velocity of the corresponding spread over the visual cortex was calculated to about 3 mm/min. A hypothetical underlying mechanism was established only a few years later by Leão (517-519), who stimulated rabbit cortex electrically and found an EEG depression spreading at a similar rate of 3 mm/min centrifugally from the site of stimulation, and suggested it might be the basis for migraine aura (520). Over decades it was suggested that typical visual aura could be attributed to such a ‘cortical spreading depression’

(CSD, see below) (513). The occurrence of CSD in humans remained hypothetical until Olesen and colleagues (640) injected ^{133}Xe into the carotid artery during human migraine aura and demonstrated a spreading alteration of rCBF. Two decades later, patients who could trigger their visual aura or who were able to get access to the study center in the early phase of a visual aura were scanned with fMRI using checkerboard stimulation (366). The change of blood oxygenation level-dependent (BOLD) signal in the visual cortex in response to this checkerboard stimulation during the course of a visual aura behaved in various aspects similarly to the CSD from the animal model (518, 519). This included a signal spread with a velocity of about 3.5 mm/min, which corresponded to the clinical prediction (506) and the CSD elicited in rabbit cortex (518, 519). This suggests that visual aura in migraine might indeed be a consequence of a CSD-like event. Hadjikhani and colleagues (366) further identified the origin of this peculiar response to checkerboard stimulation being in the visual association cortex V3A.

E. Headache phase

As described earlier perhaps the most striking symptom of a migraine attack for most patients is headache, although additional symptoms have to be present to make the diagnosis, such as nausea, photophobia, phonophobia and movement sensitivity (386). Accordingly, the imaging pattern obtained during migraine attacks always represents a combination of these symptoms with some possibly reflecting individual symptoms, such as head pain, photophobia or allodynia, and others giving evidence of the underlying mechanisms.

1. Head pain

The phenotype of primary headache disorders is far more complex than head pain alone that is for instance elicited by noxious stimulation of the skin. However, the experience of pain is present in noxious head pain and spontaneous migraine attacks, and the signature identified in functional brain imaging of experimental head pain should also be found in migraine headache. In other words, the demonstration of *additional* areas in primary headache disorders might be regarded more specific for migraine and thus might reflect symptoms other than head pain or even mechanisms driving migraine attacks. Functional brain imaging of noxious pain in the head will be discussed at this place since it greatly simplifies our understanding of functional brain imaging of migraine. Using $H_2{}^{15}O$-PET in seven healthy subjects, May and colleagues (585) measured rCBF after the injection of a small amount of capsaicin into the forehead. They found an increase of rCBF in the pain state in several brain areas including the bilateral insula, the anterior cingulate cortex, the cavernous sinus and the cerebellum. Importantly, there was no activation of the brainstem.

2. Migraine attacks

One of the most influential migraine studies of the last two decades measured rCBF using PET with ^{15}C-labeled O_2 integral inhalation in nine migraineurs during spontaneous right-sided migraine attacks. When compared to the pain-free interval, there was an increase of rCBF during migraine in the cingulate cortex, the auditory association cortex, and the parieto-occipital junction near the visual association cortex. In addition, the migraine state showed

increased rCBF in the midbrain, the dorsal rostral pons close to the PAG and raphe nuclei (842). In comparison to the non-specific pain-signature of the capsaicin experiment above (585), this study located various migraine symptoms to different areas of the brain with the experience of head pain to the cingulate cortex, photophobia to the visual association cortex, and phonophobia to the auditory association cortex. These signals disappeared after successful termination of the attack. However, the increased rCBF in the brainstem persisted in the early pain-free phase. This structure might thus not just reflect a migraine symptom but it indicates a dysfunction of importance for the generation or in sustaining of the migraine attack itself (Figure 3). The relevance of the brainstem for the pathophysiology of migraine is further supported by clinical studies and basic research. For instance, the new onset of migraine in previously non-migraineurs who have been treated with deep brain stimulation of the PAG for other pain conditions (677, 822) and the accumulation of iron in the PAG over the duration of illness (844) point to the PAG being crucial for the development of migraine. As described here in several sections, several animal studies support this view by demonstrating that brainstem nuclei, such as PAG and raphe nuclei have great influence on trigeminovascular processing in experimental migraine models (21).

More refined techniques with higher spatial and temporal resolution have led to functional brain imaging studies supporting the importance of the brainstem for migraine pathophysiology. Bahra and colleagues (66) compared migraine to another primary headache (cluster headache) and demonstrated that the brainstem activation is specific for migraine. Afridi and colleagues (13) assessed the laterality of this activation in unilateral migraine attacks.

They found it being ipsilateral to the headache side and concluded that unilateral pain might be a consequence of unilateral brainstem dysfunction. Importantly, as described above, Maniyar and colleagues (559) also found the dorsal rostral pons and the PAG, but also the hypothalamus being activated in the early premonitory phase supporting the view of a 'migraine mediator' in these areas. When combining the clinical picture of migraine being a dysmodulation of sensory: nociceptive, light, sound, and olfactory, input and the findings from functional brain imaging, brainstem or hypothalamic structures, or both, seem to be crucial for the pathophysiology of migraine and might reflect the anatomical location of brain dysfunction leading to the complex pattern of migraine attacks.

3. Photophobia

Denuelle and colleagues (208) studied eight migraineurs during headache attacks, after relief by sumatriptan and in the migraine-free interval. By applying continuous light stimulation, they found that *low luminance* stimulation resulted in an increase of rCBF as measured by $H_2{}^{15}O$-PET: there was hyperperfusion of the visual cortex during the headache attack (cuneus), after headache relief (cuneus and lingual gyrus), but not in the inter-itcal state. This might reflect hyperexcitability of the visual cortex during migraine attacks. By definition, the persistence after headache relief was *independent* of the presence of head pain. This might point to the structural correlate of photophobia being located in the primary and supplementary visual cortex. Interestingly, the areas activated *during* migraine attacks by *low* luminance were the same as the areas activated *interictally* by *increasing* luminous intensities supporting the view

that migraine and even its associated symptoms are continuously subject to a cycling mechanism.

Although conducted in the premonitory phase studies of non-headache symptoms without pain have been valuable in showing the independence of these phenomena from pain yet their important biology in migraine. It has been shown comparing patients with triggered premonitory attacks that those with photophobia, photic hypersensitivity given the lack of pain, had activation of extrastriate visual cortex (Brodman area 18) (559). In addition, interictal connectivity in the visual system is seen using resting state methods in the lingual gyrus (785). Similarly to the premonitory visual findings, when comparing patients with or without nausea in the same experimental design, those with nausea had activation in the rostral dorsal medulla in an area that included the nucleus tractus solitarius, dorsal motor nucleus of the vagus nerve and the nucleus ambiguous, as well as activation in the periaqueductal gray (PAG) (560). These studies build a picture of the brain regions involved in migraine and clearly show mechanisms that are not simply pain-dependent.

Different visual migrainous phenomenona are associated with a dysfunction of different areas of the visual association cortex. For instance, the cuneus and lingual gyrus are involved in photophobia (208), whereas V3A might be the origin of typical visual aura (366). When further comparing the imaging results during migraine premonitory phase, i.e. hypothalamic and brainstem activation with those of cortical activation during typical migraine aura, it seems likely that aura and migraine are different phenomena.

4. Blood-brain barrier

The integrity of the blood-brain barrier (BBB) in migraine is a crucial question particularly for therapeutics (see section X). It has been speculated for some time that the BBB may be disrupted in migraine (378). Schankin and colleagues (708) used a bespoke PET ligand ^{11}C-dihydroergotamine, measuring the influx rate constant Ki, average dynamic image and time activity curve using arterial blood sampling. At rest, there was binding of ^{11}C-dihydroergotamine in the choroid plexus, pituitary gland, and venous sinuses as expected from the pharmacology of dihydroergotamine (367). This was not altered in controls or migraine patients with a nitroglycerin-triggered attacks; and is broadly consistent with the known data suggesting the BBB is intact in migraine (243, 328). However, whether medicines access the brain is an entirely different question. Sumatriptan, classically considered peripherally acting, has a concentration of 10-20% the venous levels in the CSF of dog (433). After oral administration of sumatriptan 100mg in volunteers not having migraine, it could be measured in the CSF (626) in amounts sufficient for pharmacological actions. Similar discussions are had concerning gepants, calcitonin gene-related peptide receptor (CGRP) antagonists. Using ^{11}C-MK-4232, a CGRP receptor antagonist and PET ligand, it has been shown that telcagepant, a clinically proven CGRP receptor antagonist (Table 4) has low receptor occupancy (425). Lastly, it is often said, in a careless manner that monoclonal antibodies do not cross the BBB. It is clear from very careful, older studies that about 0.1% of the intravenous concentration can be found in the CSF (262). These data have recently been corroborated with ^{125}I-LY2951742 ligand study, again a clinically proven IgG4 CGRP peptide monoclonal antibody (Table 4) found again at about 0.1%

concentration in CSF versus plasma (447). There are two themes from these data: first, from a macro perspective the BBB is normal in migraine; secondly, BBB and CSF access is not an all-or-nothing principle. The real question is how much of any treatment is needed for a clinical effect in the brain. This is certainly an unresolved but important question.

F. Postdromal phase

The postdromal phase follows the end of head pain for hours or days when the patient is pain-free but still does not feel back to normal. In contrast to the headache phase and the premonitory phase, the postdrome has not been studied specifically with brain imaging. This remains a substantial opportunity and a real challenge.

IV. Anatomy of trigeminovascular pain pathways

The previous section has described what we have learned from imaging the brain in migraineurs. Distinct areas of the brain are activated suggesting a role for them in migraine pathophysiology; whether this is triggering the attack, generating the pain, or an involvement in some of the associated neurological symptoms that occur in the duration of an attack. Much has been learned from preclinical anatomical and physiological studies about the association of these different brain regions to each other, defining the involvement of specific brainstem and diencephalic nuclei and cortical areas in this network. These studies have also been able to determine how nociceptive information from craniovascular structures is processed resulting in

the perception of headache during migraine, as well as associated neurological sensory symptoms.

A. Peripheral afferent projections

The pain associated with the head in a migraine attack, including the frontal, temporal, parietal, occipital and high cervical region, is thought to be the consequence of activation of the trigeminovascular system (Figure 4). The anatomy of the trigeminovascular system has been well described over the last 70 years and this has helped to understand the pathophysiology of migraine and the distribution of its pain. The brain is known to be largely insensate, but a rich plexus of nociceptive nerve fibers that originate in the trigeminal ganglion innervate the pial, arachnoid and dural blood vessels, including the superior sagittal sinus and middle meningeal artery, as well as large cerebral arteries (594, 658, 679). Activation of these structures, particularly the dura mater, with mechanical, chemical or electrical stimulation results in headache pain very similar to the pain in migraine, as well as other symptoms associated with migraine, including nausea and photophobia (594, 658, 679). Interestingly, stimulation of sites away from these blood vessels is much less nociceptive, with correspondingly lower symptoms of headache. The nociceptive innervation of the intracranial vasculature and meninges includes non-myelinated (C-fibers) and thinly myelinated (Aδ-fibers) axonal projections, mainly through the ophthalmic (V1) division of the trigeminal nerve, but also to a lesser extent, through the maxillary (V2) and mandibular divisions (V3). There is also a neuronal innervation of the dura mater from the cervical dorsal root ganglia (563). The axon terminals of nociceptive nerve fibers that innervate the dura mater contain vasoactive neuropeptides including calcitonin gene-

related peptide (CGRP), substance P, neurokinin A and pituitary adenylate cyclase-activating peptide (PACAP) (237, 804-806) (Table 1), which are thought to be released upon stimulation causing vasodilation of dural and pial vessels (234, 662, 852).

B. Central afferent projection

There is also a central afferent projection from the trigeminal ganglion that enters the caudal medulla of the brainstem, via the trigeminal tract, which terminates in the spinal trigeminal nucleus caudalis (Sp5C; TNC), as well as the upper cervical spinal cord (C1-C2). Nociceptive Aδ- and C-fibers predominantly terminate in the superficial laminae, I and IIo, as well as deeper laminae V-VI (22, 135, 408, 541, 542, 601) of the TNC and cervical extension. Stimulation of the dural vasculature in animal models, including the superior sagittal and transverse sinuses, and middle meningeal artery, results in activation of neurons in the TNC, C_1 and C_2 regions of the cervical spinal cord – together known as the *trigeminocervical complex* (TCC) (135, 329, 334, 461). Furthermore stimulation of the greater occipital nerve also causes neuronal activation in the same regions and enhances convergent inputs from the dural vasculature (75, 76). These data suggest that the trigeminal nucleus extends beyond its caudalis boundary to the dorsal horn of the higher cervical region in a functional continuum that includes the cervical extension. This convergence of neuronal inputs into the TCC (330, 422, 463) and the convergence of inputs from intracranial and extracranial structures probably accounts for the distribution of pain perception in migraine over the frontal and temporal regions, plus the involvement of parietal, occipital, and higher cervical regions (74). Therefore the severe and throbbing nature of pain in migraine is thought to result from activation, or the perception of activation, of these

nociceptive inputs from intracranial and extracranial structures, that converge and are relayed through the TCC. Activation of these neural pathways in animal models of migraine has become a reliable way to further understand migraine pathophysiology, as well as being used to screen for potential therapeutic targets.

C. Ascending projections from the trigeminocervical complex (TCC)

All nociceptive information from craniovascular structures is relayed through the TCC, and via ascending connections to other areas of the brainstem and diencephalon, involved in the processing of pain and other sensory information. Functional physiological and tracing studies have allowed mapping of these ascending connections. Activation of these structures is thought to contribute to the perception of pain during migraine, and also to autonomic, endocrine, cognitive and affective symptoms that last throughout the entire migrainous episode.

There is a reflex connection from the trigeminal nucleus to the parasympathetic outflow to the cranial vasculature via the superior salivatory nucleus (SuS) (584). The SuS is activated by dural electrical stimulation (473), or directly from the brainstem (336), and this traverses back to the TCC via the parasympathetic outflow to the craniovasculature (25, 312). There are also direct ascending connections with other medullary pontine nuclei including the rostral ventromedial medulla (RVM), nucleus raphe magnus (NRM), parabrachial nucleus and locus coeruleus (543, 688), and midbrain nuclei, the ventrolateral periaqueductal gray (vlPAG) and cuneiform nucleus (543), with demonstrated functional nociceptive inputs from the dura mater (133, 135, 236, 330, 418, 422). Somatosensory and visceral nociceptive information from the head and

orofacial structures, via the TCC, is also conveyed directly to hypothalamic nuclei, along the trigeminohypothalamic tract, including the anterior, lateral, posterior, ventromedial, perifornical and supra-optic hypothalamic nuclei (126, 129, 556-558), and activated by dural nociceptive stimulation (85, 556). Likewise, functional dural inputs are relayed through the caudal medullary TCC, via the quintothalamic (trigeminothalamic) tract, to the thalamus (543, 579, 731, 820, 851). Specifically dural nociceptive inputs are processed in the ventropostermedial (VPM) thalamus and its ventral periphery, the medial nucleus of the posterior complex, including posterior thalamic nucleus and the intralaminar thalamus (132, 135, 346, 347).

D. Brainstem and thalamic projections to subcortical and cortical structures

The processing of pain is complex and mediated by a network of neuronal structures which include the cingulate cortex, insulae and thalamus (211, 799). The thalamus is believed to be at the heart of the central processing and integration of nociceptive information, and is regarded as a relay center for handling the incoming sensory information, and even modulating it. A so called *'Pain Matrix'*, which includes the thalamus, as well as primary (S1) and secondary (S2) somatosensory areas, anterior cingulate cortex (ACC) and prefrontal cortex, is believed to be involved in integrating all sensory, affective and cognitive responses to pain, and becomes active during nociceptive processing (211, 799). The extent to which parts of this matrix is attentional as much as a pain-related is debated (615). Other subcortical structures, which have anatomical connections to brainstem and thalamic nuclei, are known to be involved in this fluid network depending on the context of the pain, and likely contribute to the complexity of

neurological symptoms experienced by migraineurs, additional to their headache. The amygdala and hippocampus are structures likely to be crucial in processing affective and cognitive responses to pain, respectively. Retrograde tracing from the amygdala reveals projections from the parabrachial nucleus and specifically lamina I and II of the TNC (445), which may contribute to an altered emotional state during migraine, and its comorbidity with anxiety disorders and depression (130). Furthermore, indirect projections from the trigeminal nucleus, through the amygdala to the hippocampus (484), confirmed in rodents, may contribute to altered cognition. It is likely that in time, continued research will reveal the importance of these and other subcortical structures to the pathophysiology of associated neurological symptoms in migraine.

Craniovascular projections, via trigeminovascular neurons, to VPM thalamic nuclei (876, 877), have been identified and are believed to be the principal thalamic relay conveying nociceptive information to higher cortical pain processing regions (659). Other thalamic nuclei, which may also be involved in processing nociceptive craniovascular inputs includes the posterior (Po) and lateral posterior/dorsal (LP/LD) thalamic nuclei (132, 202, 632). Two recent studies have been able to trace the connections of these nuclei to the regions of the cortex that ultimately process this information (illustrated in figure 4). In rat (631) and cat (501), dural nociceptive VPM neurons projected to mainly primary (S1) and secondary (S2) somatosensory cortices, as well as the insula. These data suggest that the processing of craniovascular sensory and discriminatory information, particularly in the ophthalmic (V1) trigeminal division, is somatotopically organized to cortical regions, which may account for the ability of migraineurs to localize their intracranial

pain to specific head regions, as well as the intensity and quality of their pain. On the other hand, dural nociceptive PO, LP and LD thalamic neurons project to many functionally distinct and anatomically remote cortical regions, including S1 and S2, but also to motor, parietal association, retrosplenial, auditory, visual and olfactory cortices (631). These data suggest that the processing of craniovascular nociceptive information in PO, LP and LD thalamic neurons relay directly to cortical areas, suggesting a role in cognitive and motor deficits during migraine, as well as allodynia, photophobia, phonophobia and osmophobia.

E. Interpretation of human imaging in context

In the section on imaging studies the specific regions of the brain activated during spontaneous and experimentally-induced migraine, and their contribution to other symptoms is explored. The anatomical and physiological preclinical studies described in this section plot the pathway of nociceptive craniovascular inputs through the trigeminovascular system that project and are processed in higher pain processing centers, and parallel the findings from the imaging studies in migraineurs. Thus, there is clear translation between preclinical studies and clinical findings, with evidence of dorsal pontine and midbrain activation occurring during a migraine attack (9, 842), even during premonitory symptoms, triggered by an experimental mediator (559). Also PET imaging studies demonstrate evidence of activation of hypothalamic nuclei (209), and activation in the ACC, frontal cortex, visual and auditory cortices, as well as the thalamic nuclei contralateral to the side in which the pain is experienced (9, 66, 842). Therefore, similar processing centers to those utilized after nociceptive activation are involved, with recent work using functional connectivity approaches that describes statistical dependencies between

spatially segregated neurons (748, 755, 801). The anatomy and physiology of the pain pathways involved in migraine are well described and help us to understand their role in the pathophysiology of the generation of pain in migraine and the associated neurological symptoms.

V. Modulation of trigeminovascular pain pathways

Ascending connections from the TCC to many areas of the brain are involved in processing nociceptive somatosensory information from the head and face, and determine how it is perceived. However there are also many endogenous mechanisms that modulate trigeminovascular nociceptive traffic, which can further determine the perception of this information. As indicated in section III there is clear evidence of activation in areas of the brainstem and diencephalic nuclei before, during and after the cessation of migraine with treatment (9, 13, 66, 209, 842) that cannot be explained as solely a consequence of the pain response. Certainly descending modulation of somatosensory processing is not unique to migraine and has previously been described with respect to spinal responses. Brainstem modulation can have both a facilitatory effect, contributing to chronic pain (270) and an inhibitory influence, through supraspinal and spinal stimulation, on spinal nociceptive processing (271, 666, 703). There is still much debate surrounding the role of brainstem and diencephalic activation during migraine. Does this activation signal an area of the brain where migraine may be triggered, or is it a consequence of activation of the trigeminovascular system, which drives other symptoms in migraine?

Human imaging studies have helped us learn a great deal about the central mechanisms likely responsible for symptoms in migraine, and those involved in its pathophysiology but a limitation of human imaging studies is that they cannot dissect specific nuclei, only general regions. This often poses more questions than providing answers. However preclinical studies have been able to dissect specific nuclei that provide endogenous modulation of trigeminovascular nociceptive traffic, which may or may not also be involved in the more general modulation of pain (descending projections are summarized in figure 5). These studies may provide us with more of the answers that are necessary to determine the role of these brain areas in migraine.

A. Brainstem modulation

1. Superior salivatory nucleus (SuS)

The SuS, located in the pons, is part of the trigeminal autonomic reflex, receiving a reflex connection from the trigeminal nucleus (584). It contains the cell bodies of neurons that are part of the cranial parasympathetic autonomic vasodilator pathway (745). These neurons project predominantly through the greater petrosal branch of the facial (VIIth) nerve, via the sphenopalatine (pterygopalatine) ganglion (360) to the cranial vasculature, including the dura mater and lacrimal gland. Activation of the SuS and its parasympathetic projection to the cranial vasculature is thought to contribute to the autonomic symptoms sometimes found in migraine (26, 494), but particularly in trigeminal autonomic cephalalgias, such as cluster

headache and paroxysmal hemicranias (309). The SuS also has bidirectional connections with areas of the hypothalamus, including lateral (423, 745) and paraventricular hypothalamic nuclei (424, 688, 745) as well as the A5 and the parabrachial nucleus, and limbic and cortical areas (745). These are regions involved in feeding, sleep and stress, which may contribute to triggering mechanisms in migraine, as well as to associated neurological symptoms (131).

Studies in rodents have demonstrated that direct stimulation of the SuS activates two populations of neurons in the TCC (25, 26). First, via retrograde activation of the trigeminal autonomic reflex, within the brainstem, there are responses that are not blocked by inhaled oxygen. The second population of neurons causes activation of the parasympathetic outflow to the cranial vasculature, which indirectly activates trigeminal afferents from the dura mater to the TCC, also resulting in autonomic symptoms. Autonomic symptoms are demonstrated by increased flow in the lacrimal duct/gland. Both neuronal and autonomic responses are attenuated by inhaled oxygen and blockade of the autonomic pterygopalatine ganglion (26) (Figure 6). Furthermore, chemical manipulation of the SuS with either lidocaine or an excitant differentially modulates light-responsive TCC activity (635). Activation of the parasympathetic outflow to the cranial vasculature, through stimulation of the sphenopalatine ganglion (311, 338) and the facial nerve (304, 305) also causes increases in cerebral blood flow at the cortical level. Neurons that project from the SuS to the extracranial vasculature are believed to release vasoactive intestinal peptide (VIP) as their primary transmitter (341, 344), which is known to be released during cluster headache (320) and paroxysmal hemicrania (321), and during migraine

attacks that present with cranial autonomic symptoms (325). VIP may, in part, be the mediator of autonomic symptoms associated with these primary headaches.

There is also evidence of 5-HT_{1D} receptors and CGRP in the sphenopalatine ganglion on neurons that innervate the lacrimal gland and trigeminal ganglion (438). Therefore they are in a position to modulate trigeminovascular nociceptive activation and autonomic symptoms, which may explain why triptans can relieve symptoms in migraine, and why naratriptan is able to attenuate neuronal responses in the TCC and increases in lacrimal flow after SuS stimulation (26). These data imply that the SuS can activate neurons of the trigeminovascular system, but also modulate the responses of nociceptive inputs, as well as make changes at the level of the cortex, implying an ascending effect. Activation of these neurons is likely to contribute many of the symptoms experienced by migraineurs, including pain, cranial autonomic symptoms, and symptoms related to hypothalamic activation that are characteristic of migraine.

2. Locus coeruleus (LC)

The LC is also located in the pons and is the principle site of noradrenaline synthesis in the brain (36) and receives projections from the paraventricular hypothalamic nucleus (688). Imaging studies have indicated that dorsal pontine regions may be activated before and during migraine, which might include the LC (559). Its stimulation causes a frequency-dependent reduction in intracranial blood flow, indicating vasoconstriction, measured as an increase in internal carotid resistance (335, 336). This response is predominantly mediated by a α_2-adrenceptor mechanism (337). Furthermore, the maximal level of reduced cerebral blood flow

after LC stimulation was in the occipital cortex (319), an area where blood flow changes occurring during migraine aura are thought to begin (192, 640). Accompanying this intracranial vasoconstriction is a frequency-dependent increase in extracranial blood flow, indicative of vasodilation, measured by a drop in the vascular resistance in the external carotid (335). These responses demonstrate that brainstem nuclei can generate vascular changes in the intra and extracerebral vasculature that have been demonstrated during migraine (502), and particularly cause cortical blood flow changes similar to those found in migraine aura, which therefore may be triggered by brainstem activation.

3. Rostral ventromedial medulla (RVM)

The RVM is a cluster of neurons in the medulla. It is predominantly identified as receiving bidirectional projections from the ventrolateral PAG (vlPAG), as well as the spinal dorsal horn (80, 273, 412). This pathway is thought to provide descending control of pain processing to the spinal dorsal horn because of the high concentration of endogenous opioid signaling and has been described as the 'endogenous pain modulatory pathway' (272, 275, 573). 'ON', 'OFF' and 'Neutral' cells in the RVM, all of which are non-serotonergic (291, 292, 572), have been hypothesized to provide descending control of spinal nociceptive neurons (272, 274). 'ON' cells facilitate firing of neurons that receive nociceptive inputs, and are inhibited by opioids, whereas 'OFF' cells are tonically active and their firing inhibits nociceptive inputs, and they are activated by opioids (273). The role of 'Neutral' cells is not clear; they do not respond to noxious heat to the tail in rodents, hence their description. However they have been shown to respond to other forms of noxious stimulation to other regions of the body, including the face, in either an 'ON'

or ‘OFF’ fashion, which might indicate they are subtypes of these cells (253). The role of the RVM in the descending control of nociceptive spinal neurons may also be applied to the trigeminovascular system as well, controlling dural nociceptive inputs to the TCC. Studies have shown that RVM neurons identified as either ‘ON’, ‘OFF’ or ‘Neutral’ cells, by their response to paw withdrawal, in a lightly anesthetized state, also responded to an inflammatory soup applied to the dura mater (236). ‘ON’ cells were potently activated by the inflammatory soup with firing maintained for 105 minutes. ‘OFF’ cells were transiently inhibited during initial application of inflammatory soup with recovery after 10 minutes, and ‘Neutral’ cells were unaffected. Furthermore, in conscious animals, the dural inflammatory soup also causes hypersensitivity to cutaneous facial and hind-paw innocuous stimulation (236), caused by central sensitization of trigeminovascular neurons (132, 135) (see section VI). These responses are inhibited by application of bupivacaine directly into the RVM, locally anesthetizing descending projections to the TCC (236). These data demonstrate that dural nociceptive trigeminovascular activation activates specific neurons in the RVM, involved in the modulation of pain processing, and local changes within this region can modulate the perception of sensory stimulation and neuronal activation in response to dural or cutaneous facial nociceptive activation.

4. Nucleus raphe magnus

The nucleus raphe magnus (NRM) is at the level of the RVM and makes up part of the endogenous pain modulatory pathway described above (271), sending specifically serotonergic projections to the TCC and spinal cord in rats and cats (546, 547). It is a region that is activated

by dural nociceptive stimulation (473) and 'ON' and 'OFF' cells respond to meningeal, corneal and facial cutaneous stimulation, alongside other extracephalic inputs including tail, hind- and fore-paw (254). In the same study, intravenous treatment with naratriptan increased the spontaneous activity of 'OFF' cells after 10 and 30 minutes, while mean 'ON' cell firing activity is significantly decreased. Therefore facial cutaneous and dural meningeal stimulation, which activates 'ON' or 'OFF' cells in the NRM, as well as being activated by stimulation in other regions, may be modulated by anti-migraine treatment. Furthermore, conditioning electrical stimuli applied to the NRM inhibits dural and periorbital-evoked nociceptive neuronal responses in the TCC (498). Interestingly, cortical spreading depression (CSD), believed to be the experimental correlate of migraine aura (see Section VII), causes a significant reduction in the discharge firing in the NRM, which subsequently antagonizes the inhibitory effects of NRM stimulation on dural-evoked neuronal firing in the TCC (498). It is widely established that the NRM represents the predominant serotonergic projection to the trigeminal nucleus in the brain, which indicates that this is the pharmacology of these responses, but manipulation of GABAergic and orexinergic receptor systems in this region also differentially modulates dural-nociceptive trigeminovascular inputs. Micro-injection of lidocaine and GABA causes facilitation of dural-nociceptive trigeminovascular neuronal responses, which is mediated by $GABA_A$-receptor activation (773), as a $GABA_A$-receptor agonist causes similar facilitation, and a $GABA_A$-receptor antagonist causes inhibition of dural nociceptive responses (773). Likewise, micro-injection of orexin A and orexin B into the NRM, which is mainly an inhibitory structure, facilitates neuronal activity in the TCC, an effect that was predominantly driven by OX_2 receptors (772). It is clear from these data that manipulation of the NRM is specifically involved

in the tonic descending modulation of neuronal firing in the TCC in response to peripheral intra- and extracranial nociceptive inputs.

5. *Periaqueductal grey (PAG)*

The ventrolateral periaqueductal grey (vlPAG) has become identified with migraine pathophysiology since Weiller's (842) imaging study demonstrated dorsal midbrain activation during a migraine attack, in a region that could include the PAG. Subsequent imaging studies conducted in spontaneous or experimentally-triggered migraine have repeatedly demonstrated midbrain activation before, during and after the cessation of pain with sumatriptan treatment, in migraine (9, 13, 66, 209, 559). These studies indicate that the PAG may be involved in the pathophysiology of migraine, particularly in the modulation of trigeminovascular nociceptive responses, although the exact role of the PAG in migraine pathophysiology is hotly debated and discussed later in this section.

The PAG is a midbrain structure, within the brainstem, which makes direct projections to the medullary and spinal dorsal horn, but predominantly indirectly via the RVM, where it is believed to contribute to the descending endogenous pain processing pathway. It also makes connections with hypothalamic, thalamic and cortical neurons, which associate it with higher pain processing and potentially other associated neurological symptoms in migraine. The dorsal raphe nucleus that sits within the PAG can influence brain mechanisms in terms of blood flow (342, 343) and sleep (278). The clearest indication of the PAG's role in pain mechanisms is from studies that showed that electrical stimulation of the PAG produces analgesia in conscious

rats (685), a response which has been replicated to some extent in humans (588, 872). Therefore there is clear evidence of the PAG's role in endogenous pain modulation to spinal nociceptive processing, predominantly via the RVM. There is also clear evidence that the PAG is involved in modulating trigeminovascular nociceptive processing, particularly with dural inputs. Electrical stimulation of the vlPAG in cats causes a transient inhibition of dural nociceptive trigeminovascular neurons (474). Similarly in rats, when bicuculline, a $GABA_A$ receptor antagonist, is micro-injected local into the vlPAG, dural-evoked trigeminovascular nociceptive neurons are inhibited, as well as basal trigeminal tone (471, 472). These descending inhibitory mechanisms appear to be mediated to some extent by the P/Q-type voltage-gated calcium channel. Trigeminovascular nociceptive responses are facilitated by local micro-injection of agatoxin, a P/Q-type voltage-gated calcium channel blocker, although this response seems to be modulated by non-GABAergic neurons, as the facilitation does not block the $GABA_A$-mediated response (471, 472). As described in the 'Migraine Genetics' section, P/Q-type voltage-gated calcium channels are implicated in familial hemiplegic migraine (FHM), where a missense mutation in the *CACNA1A* gene that encodes the α1 subunit of the neuronal $Ca_V2.1$ P/Q-type voltage-gated calcium channel is present in the majority of patients (645). This mutation leads to multiple gain-of-function effects, including enhanced neurotransmission and reduced susceptibility to CSD (813). These data combined provide a suggestion of a specific genetic mutation that may cause dysfunction in the descending brainstem modulation of trigeminovascular nociceptive traffic involved in migraine.

6. Neurotransmitter systems modulating the trigeminovascular system

Descending brainstem modulation of spinal and trigeminovascular nociceptive traffic may also be modulated by different neurotransmitter systems implicated in migraine. Triptans, specific 5-$HT_{1B/1D}$ receptor agonists (310), were the first dedicated anti-migraine therapeutics, believed to act either at the cranial vasculature, or more likely, in the authors' view, at the level of the TCC (433, 435). It is worth noting that glutamatergic transmission is well established in the trigeminocervical complex with NMDA (171, 317, 516, 764) and GluK1 involvement (46), as is opioidergic transmission (761), although neither have provided clinically useful to date (Table 4, 345).

i. Endocannabinoids

Endocannabinoid (22, 24, 27, 28, 361) mechanisms have been implicated in migraine pathophysiology and may represent a potential novel therapeutic approach. When either naratriptan or CB_1-mediated endocannabinoids (Figure 7A and B) are locally micro-injected into the vlPAG they cause transient inhibition of dural nociceptive neurons in the TCC, as well as inhibiting basal trigeminal tone (24, 77). There is no effect on noxious or innocuous cutaneous facial inputs in the ophthalmic dermatome of the trigeminal nerve. Interestingly, the CB_1-mediated effects are inhibited by co-application with a 5-$HT_{1B/1D}$ receptor antagonist. These data may imply that the endocannabinoid responses are mediated by neurons, or at least within the same synapse, that may also contain 5-$HT_{1B/1D}$ receptors, and that part of the therapeutic effects of triptans, may also be mediated in the vlPAG.

Endocannabinoids are described as ‘synaptic circuit-breakers’ (459) acting as retrograde neurotransmitters in the PAG and RVM. They are released from post-synaptic sites acting on pre-synaptic CB_1 receptors to prevent the release of GABA and glutamate. The mechanism through which these neurotransmitter systems in the brainstem provide descending modulatory control of trigeminovascular nociceptive processing is not clear and we propose a mechanism through activation of ‘ON’ and ‘OFF’ cells (Figure 7C and D). In the PAG local injection or endogenous release of serotonin (or triptan) and endocannabinoids inhibit the release of GABA from presynaptic terminals, causing the disinhibition of output neurons (703), which activate monosynaptic glutamatergic projections to ‘OFF’ cells in the RVM to modulate nociception (609). It is also known that activation of post-synaptic orexin 1 receptors in the PAG stimulate the synthesis and release of endocannabinoids, resulting in retrograde inhibition of GABA release (398), which may be involved in this mechanism. At the same time we hypothesize that this descending glutamatergic projection also synapses with an inhibitory interneuron in the RVM, which inhibits activity of ‘ON’ cells, thus switching off activity at the level of the TCC second order neuron. Within the RVM endocannabinoids inhibit GABAergic projections to ‘OFF’ cells, increasing ‘OFF’ cell activity by disinhibition (597, 598). Also endocannabinoids inhibit glutamate release from glutamatergic projections to ‘ON’ cells, thus reducing ‘ON’ cell activity at the level of the TCC. There is also thought to be state-dependent and bidirectional control of pain modulation through serotonergic projections from the RVM to the TCC that is distinct to ‘ON’ and ‘OFF’ cells (269).

ii. Functional consequences of brainstem modulatory dysfunction

It is often argued that if a dysfunction of brainstem nuclei, that includes the descending pain modulatory system, is involved in the pathophysiology of migraine, which alters the perception of nociceptive activation of the trigeminovascular system, it would also affect the way that pain is processed at the spinal level. However, it has been shown repeatedly that the descending modulation of trigeminovascular nociceptive traffic seems to be different from that of spinal nociceptive processing. In the vlPAG descending modulatory effects tend to only alter dural-evoked Aδ-fiber trigeminovascular nociceptive responses, as well as basal trigeminal tone, but it does not alter either noxious or innocuous cutaneous facial responses, particularly C-fiber responses (24, 77, 410, 471, 472). However; previous studies clearly indicate that the PAG-RVM pathway provides descending control of only noxious cutaneous pinch-evoked C-fiber responses at the spinal level (836, 837), with innocuous inputs and spinal tone unaffected. In preclinical studies stimulation of cranial structures predominantly causes activation of neurons with Aδ-fiber latencies in both the TCC and VPM thalamic neurons (501, 631, 729), which project to the somatosensory cortex, and even when C-fiber intensity stimulation is used, only Aδ-fiber latency responses are identified. It is not clear why there are so few C-fiber latency responses in this trigeminovascular pain pathway that project to the cortex. It may indicate that the nociceptive trigeminovascular projections that are thought to be activated primarily during migraine are mediated predominantly by Aδ-fibers, and hence the descending modulation from the brainstem is mediated by a separate population of neurons to those that project to the spinal cord and modulate spinal nociceptive processing.

Spinal nociceptive responses appear to differ from trigeminovascular nociceptive responses, which may explain why spinal pain perception is not altered during migraine and treatment. Triptans are the classic example, they are extremely effective in the acute treatment of migraine, but carry little (823) or no analgesic properties with respect to other pain types, such as facial pain (379). In preclinical studies noxious, mechanical trigeminal neuronal responses are inhibited by naratriptan, whereas similar noxious mechanical spinal responses are unaffected (187). Furthermore 'ON' and 'OFF' cells in the NRM, that respond to noxious stimulation throughout the body, including cephalic and extracephalic regions, respond to naratriptan treatment, but as described above, we know they only relieve migraine related head-pain. It is often thought that this difference is related to the location of 5-$HT_{1B/1D}$ receptors on cranial blood vessels and at the level of the TCC. However, it is clear triptans have effects in the vlPAG (77), and indeed on trigeminothalamic neurons (730), and clearly alter neuronal responses in the NRM, which would imply they would affect pain processing in general, but they do not. It is possible that the population of neurons that project to the trigeminovascular system behave differently and respond differentially to noxious inputs, and hence the clear definition of migraine as a separate and unique pain disorder.

B. Hypothalamic modulation

Imaging studies in migraine have predominantly located activation in the midbrain, with increased activation in the hypothalamus before (559) and during (209) also demonstrated. Activation in the hypothalamus more posteriorly in trigeminal autonomic cephalalgias (339) is well described (575, 576, 580, 581). The hypothalamus is involved in a number of crucial

physiological functions including controlling the sleep-wake cycle, feeding, thirst, arousal and urination, as well as autonomic and endocrine regulation (650, 727). These mechanisms implicate it in the early origins and premonitory symptoms of migraine, where sleep disturbance (348), changes in arousal (197) and mood, food craving, thirst and urination (300) are known to occur and can increase the likelihood of an attack, as well as early symptoms.

The hypothalamus is also thought to be involved in pain processing. It has reciprocal connections with the TCC, including the trigeminal nucleus caudalis (556, 558, 688), as well as many structures involved in the processing of nociceptive inputs, including the nucleus tractis solitaris, RVM, PAG and NRM (727). Nociceptive stimulation of the dura mater activates neurons in the anterior, posterior, ventromedial, and supra-optic hypothalamic nuclei, and potentially paraventricular hypothalamic nuclei (85, 557). Hypothalamic nuclei also have descending projections to the SuS (423, 424, 688, 745), where they are thought to be in involved in autonomic regulation, and its activation may contribute to autonomic symptoms in migraine (494), and especially trigeminal autonomic cephalalgias (315), as well as contributing to further activation of trigeminal afferents from the cranial vasculature (25, 26, 635). Hypothalamic descending projections are known to be involved in the descending modulation of nociceptive inputs at the spinal level (277), and several of these descending projections have been shown to modulate trigeminovascular nociceptive processing.

1. Posterior hypothalamic nucleus

The posterior hypothalamic region is activated as a consequence of dural electrical stimulation in cat (85), and is implicated in imaging studies from both migraine and trigeminal autonomic cephalalgias. Orexins A and B are hypothalamic neuropeptides that are made solely in hypothalamic nuclei, including the posterior hypothalamic region (356) and are involved the hypothalamic regulation of sleep, feeding and arousal and the autonomic system (405, 700, 802). Intravenous orexin A is able to inhibit dural-evoked trigeminovascular transmission, but locally injected into the posterior hypothalamus, orexin A and B differentially modulate dural and cutaneous evoked nociceptive trigeminovascular responses (78). Orexin A inhibits dural electrical and thermal facial cutaneous evoked neuronal responses in the TCC, while orexin B facilitates these same responses. Given the role that both the hypothalamus and orexinergic system play in pain modulation, feeding, arousal and sleep regulation, these data provide a causal link between the possible origin for the triggering of migraine and premonitory symptoms (hypothalamus), a neurotransmitter system (orexinergic) known to be involved in the homeostasis of these triggers and symptoms, and a role of both in the descending control of trigeminovascular nociception, thought to contribute to the pain in migraine.

Another hypothalamic neuropeptide that has similarly been implicated in hypothalamic mechanisms in migraine is somatostatin that has five recognized receptor subtypes (429). It is involved in the regulation of food intake (754) and glucose metabolism by acting as a tonic inhibitor of glucagon release during by low glucose concentrations (162). Injection of a non-specific somatostatin antagonist, cyclosomatostatin, into the posterior hypothalamus, inhibits dural and facial cutaneous nociceptive neuronal inputs in the TCC (79), demonstrating a

potential role in the descending modulation of trigeminovascular nociceptive traffic. Interestingly, systemic octreotide, a somatostatin analogue agonist, was effective in the treatment of cluster headache, but not migraine (527, 577), indicating that these hypothalamic neurotransmitters may not be universally involved in all primary headaches, but certain types, demonstrating the importance of these specific descending mechanisms to their pathophysiology.

2. *Paraventricular hypothalamic nucleus*

The paraventricular hypothalamic nucleus (PVN) is a region that shows increased neuronal activation after both electrical dural stimulation in cats (85) and dural inflammatory soup in rats (557), but in both cases the data are increased without showing significance, or not increased in all animals. However clear descending projections to the TNC, particularly nociceptive laminae I and IIo, and the SuS have recently been demonstrated (688). In the same study a host of local chemical manipulations in the PVN were shown to alter dural nociceptive and basal neuronal activity in the TNC (688). Micro-injection of muscimol, the $GABA_A$ receptor agonist, into the PVN, inhibited basal and dural-evoked trigeminovascular neuronal activity. The level of inhibition was attenuated when rats had been previously exposed to a 'stress' protocol. Gabazine, a $GABA_A$ receptor antagonist, was able to facilitate dural-evoked responses. Similarly, microinjection of the autonomic and sensory neuropeptide, PACAP-38 facilitates basal trigeminal neuronal activity and after-discharges (responses greater than C-fiber latency), and the PACAP antagonist, PACAP6-38 inhibited basal and all nociceptive dural-evoked trigeminovascular neuronal responses. Finally micro-injection of naratriptan, a $5\text{-}HT_{1B/1D}$

receptor agonist, used in the acute treatment of migraine attenuated both basal and dural-evoked trigeminovascular responses. These findings demonstrate the powerful modulatory role the PVN has on trigeminovascular nociceptive traffic, and with descending projections to the SuS, it clearly has a role in modulating, or even triggering, nociceptive, autonomic and stress-related processes in migraine, and likely, trigeminal autonomic cephalalgias.

3. A11 Hypothalamic nucleus

The A11 hypothalamic nucleus is located along the rostrocaudal axis of the periventricular grey of the caudal hypothalamus (193), providing direct dopaminergic inhibitory projections to the spinal cord dorsal horn (193, 740), believed to be the sole source of dopamine in the spinal cord (413). Dopamine activation is known to alter dural trigeminovascular nociceptive responses, at the level of the peripheral dural vasculature, through dopamine D_1 receptor mechanisms (18, 156) and centrally at the level of the TCC through dopamine D_2 receptor mechanisms (89, 156). Electrical stimulation of the dopaminergic A11 projection causes a significant inhibition of noxious dural and cutaneous facial-evoked inputs in the TCC, mediated through D_2 dopamine receptors (156). However, lesioning the A11 nucleus facilitates both noxious and innocuous dural and cutaneous facial-evoked inputs (155, 156). The facilitation in neuronal firing to noxious stimuli is reversed by both 5-$HT_{1B/1D}$ and dopamine D_2 receptor agonists, but only the D_2 receptor agonist was able to reverse the facilitatory effects in neuronal firing of innocuous stimulation to the cutaneous facial region (155). In normal conditions, it is likely that the A11 nucleus provides descending tonic inhibitory control of incoming trigeminovascular nociceptive traffic through the release of dopamine, acting on dopamine D_2 receptors. During migraine it is

possible that a dysfunction of the A11's inhibitory projection to the TCC removes the tonic inhibition through dopamine release, causing a facilitation of neuronal responses and hyperalgesia and allodynia to somatosensory inputs in the trigeminal distribution. The use of dopamine antagonists is often cited as not consistent with A11 involvement, although clinically employed medicines with randomized controlled trial evidence (294), have more complex pharmacology then simple dopamine receptor interactions. Interestingly restless leg syndrome, which is believe to be caused by a dysfunction in the A11 nucleus (172), is treated with D_2 receptor agonists (644), and there is certainly a suggestion that migraine is co-morbid with restless leg syndrome (72, 686).

The data regarding the hypothalamic modulation of trigeminovascular pathways clearly demonstrate that several regions are involved in modulating basal and incoming nociceptive inputs to trigeminovascular neurons. It is possible that a dysfunction in any one of these regions may result in altered processing of nociceptive inputs that is processed and generates migrainous pain, or indeed this dysfunction could actually result in triggering activation of previously quiescent trigeminovascular neurons that is perceived as noxious activation, if these neurons receive projections from dural afferents, and is processed as migraine. Furthermore, nuclei in the hypothalamus are uniquely placed and involved in the regulation of many other homeostatic processes, such as feeding, sleep/wake, arousal, stress, that potential triggers of migraine may alter the way nociceptive information is processed, but also the triggering of migraine through the hypothalamus also results in many of the associated neurological symptoms (411). Future studies into the role of the hypothalamus in migraine are likely to

dissect further significant revelations that help us to elucidate its pathophysiological mechanisms.

VI. Thalamic processing of trigeminovascular pain

The thalamus is the major center for processing sensory nociceptive information in the brain, and relaying this information for processing in cortical structures where it is perceived by individuals. Ventroposteromedial (VPM), posterior, lateral posterior/dorsal thalamic nuclei have all been demonstrated to receive functional nociceptive inputs from the dura mater (132, 202, 632, 876, 877), and this can modulate how this painful experience is perceived. Several of the most effective acute and preventive treatment strategies are able to modulate dural nociceptive trigeminothalamic inputs, when locally applied to the VPM. Acute treatments such as 'triptans' (5-$HT_{1B/1D}$ receptor agonists) (730) and CGRP receptor antagonists (769) are able to inhibit acute dural nociceptive inputs. Likewise, the migraine preventives propranolol (729), sodium valproate (47) and topiramate (44) are also able to inhibit dural nociceptive trigeminothalamic inputs in the VPM. Targeting specifically the thalamus alters the perception of the nociceptive input coming from the periphery without the peripheral effects of drugs, which results in a reduced pain response. Additionally targeting the thalamus allows one to dissect novel effective therapeutic targets without peripheral effects, which are suitable for those patients with cardiovascular and cerebrovascular disorders. Indeed, in the topiramate study it was possible to dissect out that the major pharmacological mechanism in the VPM was via glutamatergic kainate (iGluR5) receptors, an effect that was also found at the TCC (44).

iGluR5 receptor targets have been proven to be effective in the acute treatment of migraine (448, 704), demonstrating a purely centrally mediated approach can treat migraine, with effects mediated by the VPM. Targeting the processing of trigeminovascular nociceptive information in the thalamus may represent a step forward in the development of therapeutics.

Evidence of thalamic activation during migraine is clear (9, 66), but the role it plays is thought to go beyond that of merely a relay in processing sensory nociceptive information to the somatosensory cortices. It has also been demonstrated that activation in thalamic nuclei can also contribute to the modulation of trigeminovascular and other spinal nociceptive inputs. Below we describe in detail how cutaneous allodynia; the perception of pain in response to normally innocuous stimuli, in the cephalic and extracephalic regions, is likely the consequence of sensitization of central trigeminal and thalamic neurons (132, 135). The particular contribution of the thalamus is the spread of cutaneous allodynia beyond the site of pain to contralateral cephalic and extracephalic regions via sensitization of thalamic neurons, particularly in the posterior, VPM and lateral regions. Hence the perception of somatosensory trigeminovascular and spinal inputs are altered as a result of sensitization of thalamic neurons. The authors of these studies propose that the mechanism of sensitization may be the result of a sequential sensitization of first, second and third-order trigeminovascular neurons through incoming signals coming from the peripheral dural trigeminal innervations (132, 135, 766). Although activation and sensitization of thalamic neurons via mechanisms directly through medullary, midbrain and hypothalamic nuclei, as described above, could potentially also drive this response (Section– Theories of Migraine).

VII. Cortical processing of trigeminovascular pain

In recent years evidence has been growing that migraineurs suffer an alteration in cortical excitability that may act as a susceptibility factor for migraine attacks (60, 61, 182, 505, 749). While the mechanism of how this might contribute to migraine is not known, it is certainly undeniable that there is endogenous corticofugal modulation of trigeminovascular nociceptive inputs via medullary and midbrain structures. In a recent study in rats descending projections from the cerebral cortex, specifically from contralateral insular and primary somatosensory (S1) cortices, to laminae I-II and III-IV, respectively, of the TNC were demonstrated (630), although ipsilateral functional connections have also been demonstrated (771). These descending connections have been previously shown in humans (490). Functionally it has been demonstrated that CSD, the experimental paradigm believed to represent the neural mechanism of migraine aura (Section VII), is able to inhibit neuronal activity in the NRM. Further, repetitive CSDs were able to reverse the descending inhibitory effects that the NRM has on dural nociceptive trigeminovascular responses (498), demonstrating a cortico-NRM modulation of trigeminovascular nociceptive inputs.

Cortical spreading depression is known to cause neuronal activation in the TNC, an effect that has been hypothesized to be mediated by activation of peripheral dural nociceptive trigeminovascular mechanisms (879, 880). However, CSD evoked increases in basal trigeminovascular discharge firing has been shown to be at least partly independent of a peripheral trigeminovascular action, indicating a mechanism driven within the central nervous

system (500). Further studies show that different regions of the cortex differentially effect peripheral trigeminovascular nociceptive inputs. CSD initiated in the contralateral insular cortex induced facilitation of dural-evoked neuronal responses in the TNC, whereas CSD initiated in the contralateral S1 somatosensory cortex inhibited the same responses (630). CSD initiated in the primary visual cortex enhances or inhibits dural-evoked responses, but does not affect noxious facial cutaneous-evoked responses (630). Of note, CSD initiated in the ipsilateral parietal region, an area which conveys the somatosensory and visual cortices, also causes a significant inhibition of dural-evoked nociceptive neuronal firing in the TCC in 9/30 neurons; a response that is mediated by the 5-$HT_{1B/1D}$ 'triptan' receptor (771). The remaining 21 neurons were unaltered by parietal CSD. These cortico-brainstem-trigeminal networks are positioned to influence dural and cutaneous nociception, and altered cortical excitability, believed to affect susceptibility in migraineurs, would clearly change how intra and extra-cranial somatosensory information is processed, and ultimately perceived by the migraineur.

VIII. Neural Basis for Headache Pain Quality and Associated Symptoms

As indicated by the ICHD-IIIβ (386) and outlined in section 2 specific criteria are laid out for the headache quality in migraine, and migrainous symptoms are not just restricted to headache pain but it is also accompanied by many other symptoms of the sensory system and homeostatic function that occur throughout the duration of the migraine attack. These can include hypersensitivity to sensory inputs such as light (photophobia), sound (phonophobia) and touch (cutaneous allodynia), but also symptoms caused by disruption to normal homeostatic functions such as altered sleep, feeding and even mobility. Most patients

consistently experience a subset rather than all symptoms, but each seems to be driven by similar pathophysiological mechanisms. Below we outline the likely neural basis for the headache quality, and some of the most well-known associated symptoms that accompany migraine.

A. Premonitory symptoms

Premonitory symptoms are part of the non-headache symptoms of migraine attacks. Per definition, they occur prior to the onset of headache and are different from migraine aura. In a prospective electronic diary study, Giffin and colleagues (300) assessed whether migraineurs were able to identify non-headache symptoms that could predict migraine attacks. From the symptoms entered by the patients, seventy-two percent were indeed able to do so. The most common premonitory symptoms were feeling tired and weary (72%), concentration problems (51%), and neck stiffness (50%). Less common, but importantly associated with a higher predictability of migraine attacks were yawning, blurred vision, noise sensitivity, difficulties of higher cortical function (such as reading, writing, speech, thinking), and feeling emotional and irritable. In addition, homeostatic regulation seems to be disturbed during the premonitory phase manifesting with thirst, nausea, hunger, frequent urination, or constipation (300). This complex pattern of symptoms has led to the hypothesis that the symptoms might be hypothalamic in nature and/or diffuse cerebral (106). Due to the difficulties of predicting migraine attacks, only a few basic science studies have addressed the pathomechanism of these symptoms despite the enormous implications for our understanding of migraine.

As mentioned in detail in section III, Stankewitz and colleagues (749) used fMRI after trigeminal nociceptive stimulation and found interictal reduced activation of the spinal trigeminal nuclei. This normalized prior to the next attack with even increased activation during the attack (Figure 1), although strictly not a study of the premonitory phase since the clinical phenomenology were not documented to make that distinction. Maniyar and colleagues (559) triggered acute migraine attacks with nitroglycerin and assessed rCBF in eight migraineurs using $H_2{}^{15}O$-PET. Similar to the clinical description (106, 300), they found a complex pattern of rCBF increase during the premonitory phase including subcortical (posterior hypothalamus, ventral tegmental area, PAG, dorsal pons, putamen, caudate nucleus, and the pulvinar nucleus of the thalamus) as well as cortical areas (occipital cortex, frontal, prefrontal, temporal, parietal cortex, anterior cingulate, and posterior cingulate) (Figure 2). The premonitory symptoms of the study participants were tiredness, neck stiffness, thirst, frequent urination, photophobia, nausea, yawning, and mood changes. By combining the clinical picture with the functional imaging results we can map various premonitory symptoms to specific brain areas with putative novel treatment options of migraine. A key structure seems to be the hypothalamus, which could account for yawning, frequent urination, thirst, mood changes, through connections with the limbic system; food intake, craving and changes in sleep-wake cycle. Possible neurotransmitter systems involved in these processes are the dopaminergic system (56), vasopressin (482) and the orexins, which have in part been implicated in migraine therapy (78, 284, 829, 830). Interestingly, the late premonitory phase does not show the hypothalamic activation whereas, particularly, the cortical activity does persists, and even into the headache phase (559). One speculative interpretation is that the hypothalamic involvement might ignite the migrainous

process that finally results in the dis-inhibition of the top-down modulation of the trigeminal activity resulting in head pain and thus the migraine attack (21).

B. Headache characteristics

According to the ICHD the headache in migraine has to have at least two properties that include *unilateral, pulsating quality, moderate or severe intensity and aggravation by or causing avoidance of routine physical activity* (Table 1). As discussed in section I activation of trigeminovascular pain pathways that innervate the dural vasculature is thought to be responsible for this headache quality. Studies in the 1940s on conscious patients undergoing cranial surgery confirm this (658, 679). They found that manipulation of the dura mater with mechanical distension or electrical stimulation produced pain referred to the head that was localized to different regions depending on the sites of stimulation. While this stimulation did not trigger migraine in these patients, it did cause pain referred to specific regions of the head as well as some of its common associated symptoms (658, 679). Stimulation of the superior sagittal sinus produced pain in the peri-orbital region; stimulation of the middle meningeal artery produced pain in the parietal or temporal region; and stimulation at the floor of the posterior fossa, sigmoid, transverse and occipital sinuses produced pain in the occipital region. Interestingly stimulation away from the dural vessels was much less pain-producing.

Clearly activation of axons that innervate the dural vasculature and originate in the trigeminal ganglion is painful, and produces head pain. It seems likely that activation, or the perception of activation under normal conditions, of these nociceptive nerve fibers, sometimes termed

meningeal nociceptors, which innervate the dural blood vessels is likely responsible for the severe and throbbing nature of pain in migraine. It remains unclear where that percept is processed. In preclinical studies, stimulation of the nociceptive specific dura mater (347, 497)causes much greater increases in cerebral blood flow and release of CGRP and VIP, neuropeptides known to be released in severe migraine, than after stimulation of the trigeminal ganglion (324). While no animal model can claim to be inducing migraine, preclinical animal models that use mechanical or electrical stimulation of these dural blood vessels are likely activating the nociceptive pathways involved in generating the severe and pulsatile nature of the pain in migraine, as well as neurotransmitter release coincident in migraine.

In preclinical studies mechanical or electrical stimulation of the dura mater only produces a short burst of neuronal activity in the TCC, whereas migraine pain and trigeminovascular activation is sustained for many hours These short bursts of neuronal firing are likely to represent the severe and throbbing/pulsatile quality of head pain experienced during migraine, although experimentally for only a short time. However, it is believed that peripheral and central sensitization of trigeminovascular neurons may contribute to migraine duration. In preclinical studies an inflammatory soup placed upon the dura mater is able to activate and sensitize peripheral and central trigeminovascular neurons for several hours (135, 766). This sensitization causes hypersensitivity to mechanical stimulation of the dural vasculature, including the sagittal and transverse sinuses, as well as expansion of the intracranial dural receptive field. More recent studies have shown that chemical migraine triggers, such the nitric oxide donor, nityroglycerin, also causes sensitization of central trigeminovascular neurons,

which produces hypersensitive responses to dural electrical stimulation (20). These studies demonstrate that peripheral and central sensitization of the trigeminovascular projection to the dural vasculature can exacerbate neuronal responses to innocuous mechanical and noxious intracranial dural inputs. This neural mechanism may provide an explanation for why normally innocuous physical activities such as exercise, or even unavoidable actions such as coughing, bending and taking the stairs, can exacerbate the headache in migraine, and are frequently avoided where possible. It may also add to the throbbing nature of pain in migraine as well as explaining why migraineurs tend to try to stay still as much as they can, and more often stay in bed during an attack.

C. Photophobia and phonophobia

How migraineurs commonly deal with their migraine is a clear indication of their hypersensitivity to sensory stimulation. Many patients will certainly report that during an attack they will go to bed, turn off the lights, and avoid any type of sensory stimulation from light, sound, touch or smells. As if they are shutting themselves away from all possible sensory inputs. Indeed included in the classification of migraine by the ICHD is that accompanying their migraine must be at least one of photophobia, phonophobia, nausea and vomiting (386). Photophobia in migraine may take the form of migraine pain being worsened by light, photic allodynia; where the light is itself unpleasant without pain, photic hypersensitivity. In recent years studies have begun to disseminate the likely neural mechanisms involved in their pathophysiology, specifically related to migraine (631). Findings determined that exacerbation of migraine headache requires an intact optic nerve, irrespective of visual ability. Damage to

the optic nerve prevents the exacerbation of migraine headache to light, yet blind migraineurs with an intact optic nerve can experience worsening pain as a consequence of light (632). Studies in rats were also able to demonstrate that light is able to activate specifically dural-nociceptive posterior thalamic neurons, and this activation increases with increasing light intensity (632). A subgroup of these posterior thalamic neurons receives inputs from retinal ganglion cells, and these posterior thalamic neurons project to the somatosensory, visual and associative cortices (Figure 8A). Similar findings have been made with respect to the TCC, where light can also activate nociceptive trigeminal neurons (635). The neural substrate for the exacerbation of migraine headache by light would seem to be a consequence of convergence of photic signals from the retina, via an intact optic nerve, onto dural nociceptive trigeminothalamic neurons, which subsequently project onto cortical areas (S1 and S2) involved in nociceptive processing.

As described in section III migraineurs also report a hypersensitivity or abnormal sensitivity to light, something which is likely to be the consequence of cortical hyper-responsiveness. Interictally in migraineurs luminous stimulation (600-1800 Cd/m^2) activates the visual cortex bilaterally, but there is no such activation in controls. Furthermore, when visual luminescent stimulation was combined with trigeminal pain stimulation; using heat applied to the ophthalmic region of the face, cortical activation was determined in the visual cortex in controls and it potentiated activation in migraineurs (116) (Figure 8B). During spontaneous migraine low luminescence (median 240 Cd/m^2) that does not provoke visual cortical activation outside of migraine, does cause activation during migraine, and also after pain relief with sumatriptan

treatment (208) (Figure 8C), although this activation was statistically lower than during migraine. These studies demonstrate that interictally and ictally there is cortical hyperexcitability to light in migraineurs, and convergence of trigeminovascular nociceptive inputs with photic signals, potentially in the posterior thalamic region described above (632), from where axons project to the visual cortex, may explain the neural mechanism for hypersensitivity to light in migraineurs. Given that there is cortical hyperexcitability even after pain relief, it implies that cortical hyperexcitability, and heightened sensitivity to light is not dependent on nociceptive trigeminovacular activation. Therefore modulation of cortical excitability may also be under the control of other regions of the brain relevant to migraine pathophysiology, potentially brainstem nuclei.

1. CGRP and photophobia

Biochemically it seems that CGRP may also have a role in photophobia. Genetically engineered mice with elevated expression in nervous tissue of the human receptor activity-modifying protein 1 (RAMP1), which is an important and required subunit of the CGRP receptor (694), spend less time in light environments than control littermates. In addition intracerebroventricular administration of CGRP causes a significant increase in light aversion, compared to those that received vehicle; a response that is prevented with simultaneous treatment with the human CGRP receptor antagonist, olcegepant (696). CGRP injection in control mice also caused the development of an aversion to strong light, a response that is attenuated by a triptan, 5-$HT_{1B/1D}$ receptor agonist (453), indicating that activation of endogenous CGRP receptor can drive this hypersensitive response. One possible mechanism

would be promotion of a trigeminal nociceptive pathway (635). These studies combined demonstrate the likely neural pathways involved in the development of symptoms of photophobia, and that CGRP, which is released in migraine (289, 325), contribute to these symptoms, although it is not clear at which loci the effect is driven. The neural mechanism for phonophobia has not been directly dissected. However one could readily speculate that cortical hyperexcitability in areas of the auditory cortex that are involved in the processing of sound may be involved, which receive projections from nociceptive neurons that relay via the trigeminovascular system and thalamic nuclei.

D. Nausea and vomiting

Nausea and vomiting are common features of migraine, and disturbance of food intake is frequently reported, whether this is reduced food intake from nausea, or food craving, which is often reported in the premonitory phase.

1. Hypothalamic mechanisms

The hypothalamus is regarded as the regulator of homeostatic function, and regions such as the paraventricular and ventromedial hypothalamic nuclei are known to have altered neuronal activation as a consequence of hunger or satiety as described below (See- Migraine Triggers). Furthermore, dopamine is known to have a role in nausea and vomiting, with dopamine D_2 receptor antagonists known as the classic anti-emetics, while agonists, apomorphine and piribedil both provoke increased emesis in migraineurs (92). Migraineurs also present with

increased yawning, nausea, vomiting and dizziness as a result of apomorphine treatment (109, 149). These data suggest a hypersensitivity to dopamine and its effects, and a response that is centrally mediated, as peripheral dopamine antagonists cannot reverse yawning symptoms in rats (725, 726). These studies do not suggest a locus of action, but hypothalamic regions are known to be affected by dopamine. Levels of dopamine in the ventromedial hypothalamus are known to go down as a result of feeding, and eating does not begin again until dopamine levels are re-established (596).

Alteration to homeostatic functions, which includes feeding and sleep, are also common in migraine. In a rodent model of migraine, dural inflammatory soup causes neuronal activation in the parabrachial nucleus and ventromedial hypothalamus, believed to be via sensitization of central trigeminovascular neurons (557). In half of the rats there was also activation in the paraventricular and dorsomedial hypothalamus. These animals exhibited reduced feeding 0-4 hours after the inflammatory soup placement, followed by increased feeding for the following 8 hours, as a likely compensation mechanism. Furthermore there were also increased levels of mRNA for the anorectic peptide cholecystokinin (CCK) in activated parabrachial neurons and higher mRNA for CCKB receptor in activated ventromedial hypothalamic neurons. These data suggest that central sensitization of trigeminovascular neurons activate ascending food suppressing neuronal projections, which alter feeding in these animals. It is crucial to note rodents cannot vomit, and therefore it is not a symptom that can be measured in these animals. These studies suggest that only headache mechanisms driven by peripheral inputs lead to nausea and loss of appetite, but premonitory symptoms in migraineurs, which include

nausea, suggest that these hypothalamic mechanisms may be activated without trigeminovascular activation that may lead to headache. More likely is that a single pathophysiology leads to both nausea and trigeminovascular activation.

2. Brainstem mechanisms

Brainstem mechanisms involving the PAG-RVM pathway and the role these structures have in controlling homeostatic function may also contribute to associated symptoms in migraine, such as disruption to feeding, and even sleep. These mechanisms may offer a single explanation for the contribution to symptoms of the trigeminovascular system and homeostatic function. We describe below in Section IX how continued wakefulness and skipping meals will activate 'ON' cells (65, 278, 279), which may alter the descending control of nociceptive responses to central trigeminovascular neurons, as well as connections to the hypothalamus. Through these same mechanisms associated symptoms may be generated. Certainly excessive urination, hunger, eating and food craving (or altered feeding in general), the need for sleep, and avoidance of moving around are all associated with 'OFF' cell discharge, and perhaps during migraine these responses are prolonged or exacerbated. Without doubt symptoms of altered feeding, nausea and vomiting, as well as other homeostatic processes, through the duration of migraine likely involve the hypothalamus, as well as altered dopamine levels, and are exacerbated by trigeminovascular activation and sensitization. It is also likely that connections to the brainstem PAG-RVM pathway contribute. The nature of their exact mechanisms in migraine and their contribution to symptoms is not clear but it certainly seems likely that a single pathophysiology through the brainstem PAG-RVM pathway can result in altered perception of noxious

somatosensory stimuli, as well as changes to homeostatic processes that contribute to symptoms of altered feeding and sleep through the hypothalamus.

2. Allodynia

Another aspect of pain, similar to the hypersensitivity to light and sound that patient's experience is hypersensitivity to touch, described as (cutaneous) allodynia and hyperalgesia. Allodynia: the perception of pain in response to a normally innocuous stimulus to the skin or scalp, and hyperalgesia; hypersensitivity to noxious stimuli, occurs in up to two-thirds of migraine patients (535, 723). It has been recognized at least since the 19th century (357). In migraineurs it is predominantly evident in the cephalic/facial region and pain can be provoked by simply brushing or drying one's hair, shaving or showering. It can also extend to extracephalic regions, and become an allover body allodynia, such as during dressing (127, 128). Interestingly, the frequency and severity of cutaneous allodynia is more marked in more frequent and severe migraine, and may be considered a marker for the chronification to more severe and chronic forms of migraine (95, 100). Whether it marks a process that is starting or simply reflects what has happened is unclear. Preclinical studies have helped describe the neural basis for allodynia in migraine (135, 136). Studies which used dural inflammatory soup have demonstrated that sensitization of central trigeminovascular neurons causes expansion of the cutaneous facial receptive field, as well as hypersensitive responses to brush, pressure and pinch of this receptive field (135). These responses are indicative of cutaneous facial allodynia and hyperalgesia. The development of similar hypersensitivity to innocuous and noxious inputs to the facial cutaneous peri-orbital region has been demonstrated using the experimental

migraine trigger nitroglycerin, in rodents (20). Indeed allodynia can be seen in patients triggered with nitroglycerin to have a migraine, when they report it as part of their normal spontaneous attack (Karsan, Bose & Goadsby, unpublished observations). It seems that sensitization of central trigeminovascular neurons is likely to cause referred extracranial pain as well as the hypersensitive response to cutaneous facial stimulation, and as a consequence symptoms of cephalic facial cutaneous allodynia and hyperalgesia.

i. Thalamic involvement

While peripheral and central sensitization of trigeminovascular neurons is thought to account for the facial cutaneous hypersensitivity in the referred pain region experienced by many migraineurs it cannot explain the extracephalic hypersensitivity; cutaneous allodynia and hyperalgesia which extends beyond the head and face to other regions of the body during migraine (128, 136). Central sensitization of trigeminothalamic neurons may likely to contribute to this mechanism. Preclinical studies using the dural inflammatory soup demonstrate that 50 % of thalamic neurons located in the posterior, VPM and lateral regions become hyper-responsive to noxious and innocuous inputs from contralateral cephalic and extracephalic regions (132). In patients that suffer extracephalic allodynia during migraine, BOLD imaging signals in the thalamus that are induced by brushing or innocuous heat to the hand were significantly larger when the patients were suffering with a migraine attack than before or after (132). The spread of cutaneous allodynia and hyperalgesia beyond the site of pain to contralateral cephalic and extracephalic regions is likely the result of sensitization of thalamic neurons. While the

pathophysiology of chronic migraine is not well understand (217) the frequency and severity of cutaneous allodynia may indicate that central sensitization of trigeminal and thalamic neurons becomes more common, and is perhaps less transient with little recovery between attacks. This is likely to be an avenue of research in both clinical and preclinical settings in the coming years.

IX. Aura, CSD and the Trigeminovascular System

As highlighted previously 25-30% of migraine patients suffer focal neurological symptoms (678) that commonly present as visual scintillations/scotoma, paresthesia and loss of sensation that often precede the headache by 30-60 minutes (386). Given that approximately 75% of all migraine patients do not suffer from aura, the level of attention it has received on the face of it seems disproportionate to its relative importance to migraine pathophysiology. Airy (15) drew beautifully his aura, while Lashley (506) described a slowly propagating wave of scotoma with scintillating border that drifted across his visual field at a rate of approximately 3 mm/min. Refining this further one patient recorded meticulously more than 1000 attacks that map well onto visual cortex (369). This major focus on aura, probably because of its neurological correlate, and its now believed experimental correlate, cortical spreading depression (CSD), driven by two alternative theories. (1) Aura is the initial event which triggers migraine (110) and (2) Aura is simply a parallel factor of migraine which occurs in a minority of cases (308). While the headache field continues to debate the importance of aura for migraine and its symptomology, experimental studies have been extremely important in unraveling the possible role of CSD.

A. CSD and brain injury

For some time CSD like events had not been clearly demonstrated in migraine with aura patients, despite the evidence available from cases of brain injury (259, 589, 768). In a number of patients who had undergone craniotomies for subarachnoid hemorrhage, stroke and traumatic brain injury direct cortical electrocorticography recording demonstrated repetitive CSDs, which were negatively associated with outcome. It is clear from the available clinical data that the occurrence of CSDs may have a severe detrimental outcome and this has recently been supported using experimental stroke models in familial hemiplegic migraine (FHM) mice (249). FHM mice exposed to transient occlusion of the middle cerebral artery experienced increased numbers of CSD, greater brain damage and poorer outcome than controls. Originally the association between CSD and aura was postulated based on a number of similar features including rate of propagation. More recently advances in brain imaging have enabled characteristic blood flow changes to be observed in humans, where an initial brief hyperemia (or hyperperfusion) is followed by a more prolonged oligemia (or hypoperfusion) spreading across the cortex, starting at the occipital lobe (192, 366, 636, 702). The hypoperfusion correlates with the scotoma experienced by some patients during aura (369); and it is thought the hyperperfusion correlates with the negative symptoms.

B. CSD and migraine genetics

The genetics of migraine are clearly complex and are addressed in the Section X. It is however clear from a number of studies that alterations in CSD properties are a common phenotype.

Initial studies characterizing the transgenic FHM mice which represent rare monogenic forms of migraine with aura highlighted an increased susceptibility to CSD, likely via increased cortical excitability. This increased propensity for cortical spreading depression was initially highlighted in FHM 1 (*CACNA1A*) mice (813) and later in FHM 2 (*ATP1A2*) mice (524). Despite early suggestions(586, 787), the lack of a clear link with more common forms of migraine (795), the above models of genetic susceptibility for migraine with aura have advanced our understanding of possible links between the two related conditions (795). Recently a mutation in the casein kinase 1δ (CK1δ) enzyme was found to be associated with increased prevalence of migraine with aura; interestingly a common phenotype of the newly developed transgenic mouse is also an increased susceptibility to CSD (119).

The question of the role CSD has in migraine remains, that is, does CSD predispose individuals to migraine without aura or is it simply an additive phenotype which transforms migraine without aura, to that with aura? Regardless of the ongoing debate which will only be answered by detailed translational research the impact of CSD on the trigeminovascular system is giving up its secrets.

C. CSD physiology

Cortical spreading depression (CSD) was originally described in 1944 by Leao (518, 519) as a spreading suppression of spontaneous EEG activity evoked by electrical stimulation of the rabbit cortex, and he later demonstrated that an initial depolarizing wave preceded the prolonged depression. It is now clear through a number of excellent studies that CSD results

from the depolarization, followed by a sustained hyperpolarization (or quiescence (512, 513)] of neurons and glial cells with almost a complete reversal of membrane potential resulting in breakdown of normal ionic gradients (743). Although the exact role of glial cells is unclear as blockade of astrocytic calcium waves (661) fails to block the spread of CSD indicating two parallel phenomenon. As a result of CSD the cortical microenvironment is dramatically altered with large increases in extracellular potassium and hydrogen ions along with the release of arachidonic acid, glutamate, serotonin and nitric oxide and concurrent decreases in intracellular sodium (743). Changes in perfusion that accompany the metabolic/electrocortical changes during CSD result in cortical blood flow changes: hyperemia (increased blood flow) followed by sustained oligemia **(**reduced blood flow**)** (120, 519). These changes are thought to be a consequence of neurovascular coupling where perfusion increases to meet the demand of depolarization, and decreases following the hyperpolarization or quiescence (732). However, recent data has indicated that this neurovascular coupling is impaired during the oligemic phase (665) or there may even be an uncoupling of the vasomotor and neuronal changes (120, 153), especially under conditions of brain injury (259, 589, 768). Interestingly from a clinical perspective brainstem changes may be seen with CSD in rat (616), although many antimigraine drugs do not alter it when used acutely (460). Moreover, the phenomenon is more easily triggered in female mice (121), implicating sex steroids. In additional it has been shown female mice with mutations known to produce familial hemiplegic migraine (see Section X), S218L and R192Q, are more susceptible than CSD then males (248),

It has been demonstrated, using experimental animal models, that CSD induced by mechanical stimulation; pin-prick to the cortical surface, causes blood flow changes (23, 407) that travel across the cortex, vasodilation of the middle meningeal artery and increased neuronal activity of the TCC (110). This arterial vasodilation occurs coincident with the spread of blood flow changes, but also independently, after the initial increase in blood flow. More recently electrophysiological studies have demonstrated that CSD induced with chemical, mechanical or electrical stimulation can produce prolonged activation in approximately 50% of meningeal nociceptors (879, 880), which could last for nearly two hours in some cases. If one looks at this data set as whole it would appear than CSD, approximately half the time, is able to activate neurons of the trigeminovascular system, specifically at the C1-C2 level of the spinal cord, and activation of meningeal nociceptors may contribute to the delayed dural vasculature changes that appear to be independent of CSD wave. However, this activation of trigeminovascular structures is not always observed (235, 499, 500), which may be explained by experimental and species differences, and has been observed independent of a peripheral input (500).

D. CSD and trigeminovascular activation

The exact mechanism leading to increased CSD evoked trigeminovascular throughput is like so many other aspects, still debated (62, 134, 157, 313). Interestingly, medicines used in migraine prevention can block CSD (19, 63), as does vagal nerve stimulation (163). Recent evidence suggests that localized release of molecules activates meningeal nociceptors that can drive peripheral inputs to the TCC. In one study CSD was shown to activate neuronal Panx1 megachannels, which can result in local sensitization of trigeminovascular afferents (457).

However, CSD can also evoke brainstem and trigeminovascular mechanisms without activation of meningeal nociceptors, indeed painless aura is a well-recognized concept (825). It is known to disrupt normal pain modulatory centers including the NRM (498), altering the processing of nociceptive inputs to the TCC. Direct corticotrigeminal projections have been demonstrated using a combination of electrophysiology and tract tracing. Two distinct functional networks exist (630), the first of which arises in the insula, projects to lamina I and II neurons in the TCC and facilitates trigeminovascular nociceptive tone. The second originates in the primary sensory cortex, and project to deeper TCC lamina (III and IV) and is inhibitory. The exact impact of CSD on two distinct populations of cells each with opposing effects is difficult to ascertain in the rat due to spatial localization and rapid spread of CSD. However, in gyrencephalic brains where spatial distribution is greater and CSD is thought to be more localized it is possible that individual CSDs could result in both a clear suppression and facilitation of trigeminal pain, based upon their anatomical localization.

Thus it is likely that a combination of CSD peripheral trigeminovascular activation and central pain modulatory dysregulation underlie the association of CSD/aura and migraine. Perhaps the field of migraine research has been too focused on if CSD/aura is a trigger for migraine (discussed in the theories of migraine section) with or without aura, as many triggers are known to exist and should look at the disease as a whole. As presented above, migraine occurs in three stages with a premonitory phase starting 24-48 hours before the attack long before CSD is known to occur. It is thus conceivable that a central disruption predisposes individuals to

specific triggers, of which CSD/aura is one of many which may potentiate an already perturbed system.

X. Genetics of Migraine

The existence of a strong genetic component in migraine seems obvious from clinical practice (504) and is supported by population-based family studies (695, 758). These studies show immediate family members of migraineurs have a substantially increased risk of suffering from migraine compared to relatives of matched controls (758). Interestingly, the relative risk differed depending on the presence of aura and the degree of disability. First-degree relatives of patients suffering from migraine with aura had a 4-fold increase of relative risk of migraine while relatives of patients with migraine without aura showed only a 1.9-fold risk increase (695). Further hints are provided by twin-studies that reveal a significantly higher pairwise concordance rate of migraine in monozygotic compared to dizygotic twins (295-297, 810, 811). While specific genetic changes in common forms of migraine are yet to be reported, some specific biology has been identified that does inform our understanding of migraine aura.

A. Familial hemiplegic migraine (FHM)

FHM represents a monogenic subtype of migraine with aura that involves at least one limb weakness. It does not, in spite of the name, usually involve plegia, rather weakness; the term

hemiplegic is retained for historical consistency rather than neurological accuracy. The three responsible genes currently recognized were identified by classical linkage analysis in which genetic markers are compared to a specific disease trait. All three known FHM mutations encode mechanisms that impact ion transporters, the *CACNA1A* (FHM1) (645), *ATP1A2* (FHM2) (203) and *SCN1A* (FHM3) (215) genes; their dysfunction ultimately leads to an increase in neuronal excitability (63).

1. CACNA1A

The *CACNA1A* gene was the first gene to be identified as causal for FHM1 (645). It is located on chromosome 19p13 and encodes the α1 subunit of neuronal $Ca_V2.1$ (P/Q-type) voltage-gated calcium channels (845). All known FHM1 mutations induce gain-of-function effects as they enhance channel open probability thereby increasing neurotransmission (368, 664, 798). Two mouse models; R192Q (813) and S218L (797) transgenic mice, have been developed to gain insight into the functional consequences of these mutations through a large amount of preclinical *in vivo* studies. Findings from these animal studies have substantially enhanced the understanding of migraine aura.

2. ATP1A2

The second FHM gene, *ATP1A2*, is located on chromosome 1q23 and encodes the α2 subunit of sodium-potassium pumps (203, 784). Until now over 30 mutations within the *ATP1A2* gene have been associated with FHM2. All of them induce a loss-of function on sodium-potassium ATPases increasing the potassium ion levels within the synaptic cleft.

3. SCN1A

Mutations within the *SCN1A* gene located on chromosome 2q24 represent the underlying cause for FHM3 (215). The gene encodes the α1 subunit of neuronal $Na_V1.1$ voltage-gated sodium channels. Genetic mutations within the *SCN1A* gene that have been associated with FHM mostly exert a loss-of-function effect that mainly affects inhibitory neurons although gain-of-function effects have been described.

Finally, in many patients suffering from hemiplegic migraine none of the three known FHM mutations can be identified, especially in cases without familial clustering (268). These cases of so-called sporadic hemiplegic migraine (SHM) (791) indicate that other genetic abnormalities may exist in the pathogenesis of SHM (786). If these involve other unknown FHM genes or a specific combination of other multiple low-risk genetic variations is not known (657).

4. Pathophysiology of FHM

All known FHM mutations encode proteins involved in ion transport and lead to higher concentrations of glutamate and potassium in the synaptic cleft increasing neuronal excitability which may increase the susceptibility for the induction of CSD and thereby migraine aura, which is believed to be the underlying cause of the transient motor deficit occurring in hemiplegic migraine (63). However, it is still likely that other factors such as increased incoming neuronal signals from the periphery or hormonal changes, that may affect neuronal activity, may play a role or even be required for inducing CSD even if an increased susceptibility resulting from the FHM mutations exists. Whether functional consequences go beyond the increased propensity of CSD, for instance if in affected migraineurs CSD induces activation of nociceptive pathways

involved in the pathogenesis of migraine, has not been entirely clarified. Certainly FHM1 mice have reduced calcitonin gene-related peptide expression in the trigeminal ganglion (578). Consistent these data, Fos protein expression in FHM1 mice, when subject to dural stimulation, is not increased or altered by a triptan, as it is in wild-type mice. In contrast, FHM1 mice display enhanced transmission in thalamus (654). Moreover, it can be shown in rat that transcranial magnetic stimulation, which is effective for acute migraine with aura (537) and probably as a preventive when used regularly (94), can block CSD effects on trigeminothalamic neurons after a single pulse (45). These data suggest the burden of FHM1 pathobiology may be thalamic.

5. Triggering and FHM

One important, and as yet unexplained feature of FHM, is its lack of sensitivity to otherwise typical migraine triggers, such as nitric oxide donors (374, 376) or CGRP (375). This is not simply a matter of the aura phenotype, since both nitric oxide donors (441) and CGRP (372) trigger migraine without aura attacks, predominantly, in patients with simple migraine with aura. Rarely, aura can be seen triggered by NO-donors (12); this is the exception. It has also been shown that evoked potential habituation in FHM differs from other forms of migraine (370), although interestingly FHM patients identify similar trigger factors for their attacks as migraine with aura patients (371).

<u>B. Casein Kinase 1δ (CK1δ)</u>

In clinical practice migraineurs commonly report that abnormal sleep may trigger migraine attacks and that migraine leads to an abnormal sleep pattern (859, 860). Attacks frequently

start in the early morning (399), a time in which affected individuals usually are in their REM sleep phase or shortly after waking up. In addition, changes in wakefulness may be part of the premonitory symptoms of a migraine attack. These observations and the fact that migraineurs show a higher incidence of narcolepsy (194, 195) suggest that migraine may be linked to circadian mechanisms.

A missense mutation in the gene encoding casein kinase 1δ (CK1δ) has been linked to migraine (119, 863). The *CK1δ* gene is a ubiquitous serine-threonine kinase involved in the regulation of sleep patterns. A missense mutation in the DNA-sequence of the *CK1δ* gene results in a threonine-to-alanine alteration at amino acid 44 (T44A) of the protein leading to reduced enzyme activity. This genetic alteration and its functional consequences lead in humans, and transgenic mice with the human mutation inserted, to the clinical phenotype of the Familial Advanced Sleep Phase Syndrome (FASPS), which is characterized by an abnormal sleep pattern consisting of early sleep times and early-morning awakening (794, 864). In six individuals of one family the genetic alteration has not only been associated to familial advanced sleep phase syndrome (FASPS) but also to migraine with and without aura (119). This observation suggests that beyond being a central element in the regulation of sleep, CK1δ may be functionally relevant in migraine pathophysiology. A second missense mutation with a histidine-to-arginine change at amino acid 46 of the *CK1δ* gene has been identified to cause reduced enzyme activity and co-segregate with FASPS and migraine highlighting its potential functional relevance in both disorders (119).

To assess their functional relevance in migraine, a series of *in vivo* studies have been conducted on transgenic *in vivo* models with mice carrying the T44A mutation (119). These studies revealed that compared to their wild-type littermates, mice carrying the T44A mutation show increased hyperalgesia after intraperitoneal injection of nitroglycerin, a substance known to induce neuronal activation in the dorsal horn in mice and migraine attacks in migraineurs. Mice carrying the *CK1δ-T44A* gene also show a reduced threshold for the induction of CSD as well as an enhanced vasodilation of meningeal and cortical arteries following CSD. The latter is interesting in the context of CK1δ playing a role in glutamatergic transmission (164). Moreover, mice with the T44A mutation display a similar reduced trigeminocervical complex activation profile (400), as that cited above for FHM1 mice (654), linking in some respects the migraine-related biology of these two very different mutations. These observations suggest a pathophysiological influence on migraine aura and its functional consequences. Taken together, these preclinical and clinical findings suggest that mutations in the *CK1δ* gene may contribute to the pathogenesis of migraine and migraine aura.

C. TWIK-related spinal cord potassium channel (TRESK)

A candidate gene approach led to the identification of the frameshift mutation F139WfsX24, encoded within the *KCNK18* gene, which prematurely truncates the TRESK protein to 162 residues inducing a complete loss-of-function, in a large multigenerational family affected by migraine with aura (493). The influence of TRESK on neuronal resting membrane potential, its wide distribution throughout the CNS, its functional implication in pain pathways and the segregation with migraine with aura led to the conclusion that the *KCNK18* gene may be

functionally involved in the pathogenesis of migraine, and the TRESK channel even represents a potential therapeutic target. This hypothesis has been supported by the fact that two-pore domain (K2P) potassium channels, such as the TRESK channel, are targeted by several volatile anesthetics leading to its activation. Investigation of mutant TRESK function points towards altered hyperexcitability in trigeminal ganglion neurons (540) and further that TRESK channel openers can reverse this hyperexcitability and may hold potential as therapeutic targets (365). However, further studies have revealed that other genetic mutations that also cause a complete loss-of-function of the TRESK channel do not specifically segregate with migraine (48) have raised doubt on the functional consequence of mutations within the *KCNK18* gene that lead to a dysfunctional TRESK channel, in regard to the pathogenesis of migraine. Nevertheless, the influence of K2P-channels on neuronal excitability and on pain pathways may warrant further studies to investigate their potential as a therapeutic target.

D. Genome wide association studies (GWAS)

In recent years GWAS have identified a series of single nucleotide polymorphisms (SNP) that may be relevant for the pathogenesis of migraine (53, 54, 159, 160, 283). GWAS are based on the hypothesis-free analysis of a large amount of SNPs in relation to specific disease traits. The advantage of this technique lies in the fact that compared to other genetic approaches a large number of genes can be analyzed with respect to a specific disease. However, due to the large amount of tests, GWAS are associated with several caveats inherent to the technique. Results have to be cautiously corrected for multiple testing and only associations with *p*-values below 5 x 10^{-8} can be considered significant (250). Furthermore, the identified genetic variants are

characterized by a very low relative risk questioning their clinical significance. In contrast, if high-risk genetic variants exist which show only marginal allele frequency, a GWAS approach will likely miss this genetic association. Finally, GWAS do not capture interactions between allele variants that may be functionally relevant. As a result of these difficulties, conclusions regarding the relevance of GWAS findings for the pathophysiological mechanisms of migraine and their clinical significance, especially conclusions on an individual genetic risk, have to be interpreted with caution. Therefore an identified association should always be confirmed in independent case-control studies before any conclusions are drawn.

Regardless of these technical considerations, three GWAS have been published with respect to migraine (53, 54, 159, 160, 283). These studies identified a series of potentially migraine-relevant susceptibility genes that are involved in glutamatergic neurotransmission (*MTDH*, *LRP1* and *MEF2D*) and are functionally involved in pain-sensing pathways (*TRPM8*), neuronal development (*MEF2D*, *ASTN2*, *PRDM16*, *PHACTR1* and *TGFBR2*) and brain vasculature function (*PHACTR1* and *TGFBR2*). Among these genetic variants the most consistent results have been observed for *LRP1* and *TRPM8*. While *LRP1* encodes a lipoprotein involved in nociceptive glutamatergic signaling (147), *TRPM8* encodes a cold-sensitive calcium channel that may induce burning pain (84, 592, 656). The TRPM8-channel is expressed on unmyelinated C-fibers and myelinated Aδ-fibers (477) and may co-express with TRPV1-channels and CGRP (212). Beyond peripheral sensory neurons (477), the TRPM8-channel has been identified on the trigeminal (2) and dorsal root ganglia (431) indicating a functional relevance in migraine. However, despite

these anatomical observations further *in vivo* studies are required to elucidate the functional consequences of mutations within the *TRPM8* gene.

A challenging and exciting observation for the future is an initial finding of the SNP, rs2651899 in *PRDM16* has an odds ratio of 2.6 in predicting triptan efficacy in acute migraine treatment (168). Such a result suggests the eventual possibility of personalized medicine for the treatment of migraine.

Taken together, recent data suggests that in contrast to FHM, which appears to be a monogenic disease, common forms of migraine are likely to be the result of several genetic factors which interact with each other and with environmental influences which finally lead to an increase in the susceptibility of migraine.

XI. Neural basis of migraine triggers

Migraine attacks are generally considered spontaneous in nature and sometimes thought of as occurring without any tangible trigger or precipitating factors, yet many patients will frequently report known exogenous or endogenous factors they believe to reliably trigger their migraine attacks, or at least increase their likelihood of occurring (504). Perhaps this confusion and the distinct lack of clarity about if and what factors can be involved in precipitating migraine attacks is a consequence of two major observations. First, it is likely that the entire phenotype and duration of the migraine syndrome is misunderstood by patients, but sometimes also by clinicians. The migraine attack does not begin at the perception of head pain, or in the case of

aura, during the first neurological aura deficits, but most likely 24-48 hours prior to these symptoms, during the premonitory phase (300). As described in the earlier sections, many patients will report having a feeling that a migraine is coming even though they are not in pain several days before the headache, and this is often characterized by specific symptoms, such as tiredness, lack of attention, and food craving (300). Indeed, imaging studies have demonstrated that there are significant changes in brain activation while these symptoms are perceived (559, 749). It is possible that a blurring of the lines between premonitory symptoms and migraine triggers has led patients and clinicians alike to believe that certain environmental factors believed to precipitate their migraine attack actually represent a symptom of their syndrome, such as craving certain foods, including chocolate and cheese, as well as tiredness. The other factor which complicates this issue is that there are very few controlled studies that have actually dissected internal or external events triggering attacks. One recent interesting study, which controlled both bright light and/or strenuous exercise as a triggering mechanism for migraine with aura, only produced modest predictability, in patients who self-reported these factors as triggering their attacks (427). This is not to say that certain factors do not trigger migraine attacks, or at least increase the likelihood of an attack occurring, and the volume of patients that describe, for example, skipping meals, sleep disturbance and stress as precipitating factors cannot be ignored. Perhaps the truth is closer to what we cannot see, or easily measure on a day to day basis, and down to the natural fluctuations in neuronal excitability in the brain that have been observed (750). The brain may be naturally protected at times of lower excitability, but much more susceptible to triggers at the peak of excitability fluctuations. Despite this lack of clarity there are still certain environmental and endogenous

factors known to increase the likelihood of precipitating an attack that warrant discussion of their neural basis.

A. Chemical triggers and inflammation

Environmental or experimental chemical triggers of migraine have proven, over the last 25 years, to be the most reliable approach for experimentally triggering migraine in the clinical setting (441). A number of molecules are accepted to trigger migraine (386). These are largely vasoactive and many are present at the nerve endings of perivascular nerve fibers innervating the cranial vasculature from the sensory, parasympathetic and sympathetic nervous systems (Table 2), and be released as a consequence of activation, although not all appear to be released during migraine.

1. Triggering and vasodilation are uncoupled

Nitric oxide (NO) donors, such as nitroglycerin (NTG), are highly volatile vasodilator agents (606), and have been recognized to trigger migraine for some years (515, 673). NTG-triggered migraine has been well described for many years as a model system (441) and has been the most studied preclinically. It produces an immediate headache in almost all subjects, but also a delayed migraine, after two-six hours, in migraineurs. Similar responses have been demonstrated with CGRP, PACAP and prostaglandin E2 (PGE2) and I2 (PGI2) (52, 58, 508, 720, 849). The mechanism for triggering these migraine attacks is still speculated upon. A common denominator is that they all cause immediate vasodilation of extracerebral blood vessels (52,

58, 639, 641, 642, 720, 849), and the reversal of vasodilation with sumatriptan aborts migraine (59, 440). Similar findings have been demonstrated preclinically in rats, with NO donors, CGRP, PACAP, PGE2 and PGI2 (29, 111, 622, 623, 767, 852) all causing meningeal vasodilation.

However, evidence of vasodilation as a cause of pain in migraine has now been effectively excluded. Human studies show no meaningful change in external carotid branches (40, 58, 713), and never demonstrated a temporal relationship between headache resolution and vascular changes with sumatriptan (531). Furthermore, both vasoactive intestinal polypeptide (VIP, 674) and prostaglandin D (848) are clear examples of vasoactive mediators causing immediate vasodilation and mild headache in healthy controls and migraineurs, but no occurrence of delayed migraine. In contrast pituitary adenylate-cyclase activating peptide (PACAP), which shares VIP receptor targets (83), is equi-efficacious in terms of vascular effects (39), and does trigger migraine (720) in patients. These data conclusively demonstrate that vasodilation is not an obligate component of migraine pathophysiology, and that the mechanism by which these substances trigger is not vascular.

2. Inflammatory mechanisms do not explain migraine therapies

There is some evidence that migraine triggers may stimulate inflammatory processes, which are responsible for activating a cascade of events involving sensitization of meningeal nociceptors, resulting in migraine headache. NTG administration causes delayed release of inflammatory mediators from the meninges (682) in rats, which are involved in activating and sensitizing meningeal nociceptors, which has been hypothesized to promote pain in a migraine attack (91).

PGE2 is used in the inflammatory soup that is placed on the dura mater, which induces peripheral and central sensitization (135, 766) and dural PGI2 produces peripheral sensitization of meningeal nociceptors (881). These data potentially point to a mechanism of dural inflammation and activation of meningeal nociceptors to trigger the migraine attack. NTG also produces an up-regulation of dural mRNA for inducible nitric oxide synthase (iNOS) followed by protein expression 4-10 hours after NTG, as well as plasma protein leakage that are suppressed by iNOS inhibition (682).

In contrast, iNOS inhibitors are ineffective in clinic either as an acute or preventive treatment strategies (403, 649), and likewise plasma extravasation inhibitors have also failed in the acute treatment of migraine (233, 691). Other evidence further indicates that dural inflammatory mechanisms are unlikely to be the triggers for the migraine attack. CGRP and PGE2 are well-known inflammatory mediators, but at supramaximal doses known to cause vasodilation, neither was able to induce dural plasma protein extravasation in rats (566). Furthermore, an iNOS inhibitor was unable to inhibit either neurogenic or CGRP-induced vasodilation of meningeal vessels (31), a model that has proven predictive of therapeutic efficacy (88). Finally, PACAP is known to be released upon inflammation to protect neurons and is thought of as anti-inflammatory (835). These data imply that dural inflammatory mechanisms are unlikely to be involved in triggering migraine with these vasodilator agents, although as yet only neural mechanisms have been identified in the laboratory in terms of trigeminocervical inhibition (17).

3. Brain mechanisms and triggering

If neither dural vasodilation nor inflammatory mechanisms are responsible for triggering the migraine attack after administration of vasoactive agents, other neural structures along the trigeminovascular pathway must play role. Perhaps inside the brain is where the answers lie. Premonitory symptoms, accompanied by activation of dorsolateral pons, midbrain and hypothalamic regions, have been demonstrated in NTG-triggered migraine (13, 559), prior to any description of headache, suggesting that brainstem and diencephalic nuclei may be involved in the migraine triggering process. One would anticipate that if peripheral vascular or neurovascular mechanisms through inflammation and activation of meningeal nociceptors, are involved in triggering migraine with chemical triggers, pain should be the first symptom reported as a consequence of central trigeminovascular activation, rather than occurring after other neurological deficits. This gap in trigeminovascular activation is also demonstrated in rodents, where NTG causes activation in the mid brain vlPAG, locus coeruleus and parabrachial nucleus, as well hypothalamic nuclei, before any activation in the TNC is detected (782, 783). Furthermore changes to levels of PGE2 and cyclo-oxygenase-2 in the rat brain after NTG occur in the hypothalamus prior to changes in the lower brainstem (821).

So are these migraine triggers activating nuclei in the brain involved in triggering an attack? Locally applied NO donors, including NTG, excite central trigeminovascular neurons (495, 496), demonstrating a direct effect of these molecules in the TCC and VPM thalamus. These data point towards a more neuronal basis to the triggering mechanism of these vasoactive mediators. Perhaps electrophysiological studies provide the clearest example of the systemic effects of migraine triggers on central trigeminovascular neurons. Messlinger and colleagues

have demonstrated that the NO donor, sodium nitroprusside produces a biphasic response on meningeal nociceptive central trigeminovascular neurons, with an initial increase in basal firing that accompanies sodium nitroprusside administration, but a delayed and prolonged facilitation for up to two hours (480). These effects are reversed by systemic administration of the CGRP receptor antagonist, olcegepant (481). This effect is most likely to be on second order central trigeminovascular neurons, as local cranial dural inhibition of CGRP receptors does not inhibit spinal trigeminal neurons (276), particularly as there is no evidence of CGRP receptors on peripheral axons, although they are present of central projecting axons (523). More recently we have also demonstrated with NTG that the delayed facilitation of basal trigeminal tone is prolonged beyond three hours, and there is also sensitization of noxious and innocuous responses to dural and cutaneous facial stimulation (20).

Locally applied CGRP also causes excitation of both central trigeminovascular (760) and VPM thalamic nociceptive neurons (769), and olcegepant inhibits glutamate-evoked firing in these areas. Furthermore, locally applied CGRP or olcegepant in the vlPAG, activates or inhibits, respectively, dural nociceptive trigeminovascular responses (668). However, given systemically CGRP does not activate or sensitize peripheral meningeal nociceptors, for up to one hour (526), which implies a peripheral neural mechanism of action is unlikely, although observations have not been made beyond this time frame. However, central trigeminovascular responses do seem to be transiently sensitized to facial vibrissal innocuous inputs after CGRP, although these responses were largely low threshold mechanoreceptors outside of the ophthalmic dermatome (188). However, the longer term effects of CGRP, beyond one hour, on central

trigeminovascular neurons, which would mirror its delayed effects in migraineurs is not known. In general it seems that vascular, and also likely, peripheral neurovascular mechanisms do not play a role in triggering migraine as a result of vasoactive agents. Indeed the vascular effects may be better described as a 'red herring', which distracts attention from their likely mechanism of action inside the brain. These data point to a neuronal mechanism of activation involved in triggering a migraine attack. One last and important factor that needs to be considered is that, other than NTG, which is highly volatile and readily diffuses into tissue, including the brain, CGRP, in particular, is a large peptide unlikely to cross the blood-brain barrier and therefore it is thought they cannot get into the brain to have an effect. PACAP on the other hand has a specific pump mechanism to facilitate its transport (69). It is interesting that triggers of all sorts are only effective in migraneurs, whose brain biology certainly appears to be different to healthy controls; whether this alters their ability to enter the brain can only be speculated upon.

B. 'Skipping meals'

It is generally accepted that metabolic disturbances, such as fluctuations in water balance, food intake, mood and sleep contribute to migraine in some patients (228, 300). According to some studies, lifetime migraineurs experience headache attacks preceded by triggering factors such as food deprivation and/or fasting (skipping meals) (196). Although it is debated whether fasting is actually a headache trigger or rather that food craving is a symptom in the premonitory phase of migraine. Blau and Cumings (108) attempted to identify a correlation between blood glucose and migraine, rather than fasting itself, and reported that fasting

caused headache in 50% of migraineurs. The authors proposed “some patients have some of their attacks of migraine fired off by missing a meal, and that this is related to a low blood sugar, which must persist in that individual for a certain length of time to cause headache”. Although there are many observations of food cravings during the premonitory phase of migraine, with researchers reporting that some patients would crave for sweet foods (228), and one study, using individual electronic diaries, reported that 18% of the patients reported hunger or food craving as triggers of their headache (300). These studies clearly demonstrate a blurring of the lines between altered feeding as either a cause or a symptom in migraine.

Some authors have tried to reconcile these two migrainous attributes, with Martin and Seneviratne (568) offering an explanation for their finding that food deprivation caused headache in 58% of patients with frequent migraine or tension-type headache. The authors write that “hunger arising from low blood sugar levels, for example, may lead to cravings for particular foods such as chocolate, on the one hand, and lead to headaches, on the other hand, but the headaches may be erroneously attributed to the food consumption rather than the low blood sugar levels”. Perhaps what these studies demonstrate most is the importance of alteration of the feeding schedule, either skipping or delaying meals, in migraineurs, as it clearly has an impact on the phenotype of patient suffering.

What is understood about the neural mechanisms that regulate feeding is that they are controlled within the hypothalamus (742, 869), a brain structure that we know to be active and involved in migraine pathophysiology (21, 559), and this structure is likely to impact our

understanding of the role of altered feeding in migraine. The hypothalamus is a major center of convergence and integration of several nutrient-related signals and, thus, hypothalamic neurons are thought to promote the homeostasis of physiological systems involved in synchronization of circadian rhythms, salt balance, appetite and energy expenditure, thirst and water balance, among other functions (690). A summary of the hypothalamic pathways and neuropeptides involved can be found in figure 9 and the subject is extensively reviewed elsewhere (220, 742, 869)

1. Anatomy of feeding and fasting

i. Hypothalamic-based mechanisms

Two populations of neurons located in the hypothalamic arcuate nucleus, one expressing the orexigenic neuropeptide Y (NPY) and agouti-related peptide (AGRP), which promote feeding, and the other expressing the anorexigenic peptides proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), which cause a loss in appetite, are the primary integrators of nutritional information, being sensitive to signals of energy availability (reviewed in 55, 220, 742, 869). Leptin is also one of the most important regulators of energy balance since arcuate POMC and AgRP/NPY neurons are targets of leptin with opposing signaling effects: AgRP/NPY neurons are inhibited by leptin (81, 717), in contrast to POMC neurons which are excited (718). Likewise, orexins A and B are also involved in feeding regulation in the arcuate nucleus, where orexin A activates NPY-containing neurons to promote feeding (866). As well as the interaction between NPY/AgRP and POMC/CART neurons, arcuate neurons also

project to other key hypothalamic nuclei, such as the paraventricular nucleus (PVN), dorsomedial nucleus (DMH), lateral (LH) and ventromedial (VMH) hypothalamic nuclei, orchestrating adaptive responses to energy homeostasis imbalance (reviewed in 73). These are all regions known to be relevant to migraine pathophysiology. A summary of orexigenic and anorexigenic neuropeptides and their roles in homeostatic function can be found in Table 3.

ii. Brainstem mechanisms

Outside the hypothalamus, the nucleus tractus solitarius (NTS) and the VTA are also known to be involved in feeding control and pain modulation. Leptin receptor ObRb mRNA is present in the NTS (599) and leptin causes neuronal activation (251). NTS neurons project to the VTA, PAG and LC (293), and the NTS, along with the arcuate nucleus, is the only source of anorexigenic POMC neurons (442). Injection of anorexigenic neuropeptides into the NTS reduces food intake, and antagonists increase food intake (362, 850), with 75% of NTS neurons firing in response to blood glucose fluctuations (870). The VTA is implicated in modulating food craving behaviors (600), as well as the drive to access highly palatable foods (3, 4) and increased leptin signaling in the VTA decreases food intake and firing rates of DA neurons (287, 414).

2. Neuropeptides during feeding and fasting

i. Orexins

Orexins are made solely in the hypothalamus (356), but particularly in the lateral, posterior and

paraventricular nuclei of the hypothalamus (356, 700). Intracerebroventricular (ICV) or direct micro-injection into the arcuate nucleus stimulates food intake (383, 619, 701) and this response appears to be predominantly mediated by OX_1 receptors (741). During fasting and hypoglycaemia there is increased orexin release in the hypothalamus (141, 142, 458, 701), accompanied by an increase in OX_1R receptor mRNA expression in the VMH and increase in OX_2R mRNA expression in the arcuate nucleus (551). Orexins have a close relationship with glucose metabolism, with orexin cells stimulated by low glucose levels and elevation in glucose levels suppresses both spontaneous and evoked firing in orexin neurons (125). ICV (871) or systemic injection (633) of OxA causes an increase in plasma glucose levels, and peripherally administered OxA increases insulin secretion (633).

In the context of migraine, OxA and B levels are lower in the periphery during episodic migraine, whereas OxA levels are increased in chronic migraine (706). Therefore there is evidence of a potential perturbation of the orexinergic system in different migraine states. Preclinical studies demonstrate that systemic OxA inhibits dural-evoked trigeminovascular nociceptive neurons, predominantly via Ox1 receptors, whereas OxB has no effect (408, 409). A dual orexin receptor antagonist (DORA-12), which has equal affinity to both Ox1 and Ox2 receptors is also able to inhibit dural-evoked trigeminovascular nociceptive responses (402). However, a DORA was ineffective as a migraine preventive when dosed daily, although sedation was more commonly seen as a side effect in the active then the placebo arm (150).

ii. Neuropeptide Y (NPY)

The other main orexigenic neuropeptide is NPY, which is known to be involved in regulation of the cardiovascular system, pain modulation, appetite control and circadian rhythm synchronization, and is abundantly expressed in the basal ganglia, limbic system and hypothalamus (7). It is synthesized in the arcuate nucleus (67) and released into the PVN and LH (123, 753), where it exerts its appetite stimulating properties. ICV injection or direct micro-injection into the PVN causes stimulation of food intake (751). This response is regulated by OxA activating (866) and leptin inhibiting (756, 832) NPY-containing arcuate neurons. These NPY neurons also project to many pain modulating nuclei in the brainstem, including the PAG, DRN, NRM, LC and NTS (737), and NPY Y_1 knock-out mice show increased nociception (485) and intra-arcuate administration of NPY exerts an antinociceptive effect in intact rats and in rats with inflammation through NPY Y_1 receptor activation (530). During fasting or food restriction there is increased NPY release in the hypothalamus (846), including the PVN (455), where NPY Y_1 expression is also increased (862).

In the context of migraine, evidence of altered NPY levels is conflicting. One study shows lowered peripheral levels in episodic migraineurs (146), whereas a study that measured plasma from the extracerebral circulation found no changes during the headache phase (325). However, it is a common theme in migraine that interictally brain activation is lower, yet ictally activation appears to be normalized, and it is perhaps this relative change between states that is important rather than direct comparisons to healthy subjects. NPY Y_1 and Y_2 receptors are

present in human trigeminal ganglia (807) and NPY Y_1, Y_2, Y_4 and Y_5 are present in the rodent TCC (655). In preclinical studies intravenous NPY inhibits dural-evoked neuronal firing in rats, a response that is mediated by the NPY Y_1 receptor (570). These data indicate that NPY can alter trigeminovascular nociceptive transmission.

iii. Leptin

The main anorexigenic peptide is *leptin*, which is secreted by the adipose tissue and transported to the brain where it crosses the blood-brain barrier (285, 841). In the brain it acts on ObRb, the long form of the leptin receptor (175, 252, 621, 721, 781). Circulating leptin is thought to be an indicator to the CNS of total body energy stores (282). When injected either iv, or icv, leptin activates neurons in the PVN, ARC, VMH and DMH (252, 255, 256, 815), and suppresses feeding (733). During fasting, serum levels of leptin decrease, normalizing after refeeding (478, 608). Leptin activates the food suppressing POMC pathway, and actively inhibits the orexigenic AgRP/NPY pathway, and during fasting this effect is reversed.

There is also evidence of perturbations in leptin levels in migraineurs, with increased leptin and insulin levels in one study (90), but lower serum levels interictally in another (364). There is evidence of leptin receptor (ObRb) mRNA in neuronal cell bodies of trigeminal motor nuclei as well as the LC, dorsal vagal complex and parabrachial nucleus (363). Preclinically, leptin causes a moderate but significant reduction in firing of dural-evoked trigeminovascular nociceptive neurons (569).

3. Implications for migraine

i. Brain mechanisms, migraine and feeding

The relevance of these structures to migraine pathophysiology, and specifically the ascending projections to the trigeminovascular system and descending control of trigeminovascular nociceptive transmission has been described in detail (Section V). Briefly, it has been shown that nuclei in the region of the hypothalamus are active before (559) and during migraine headache (210). There is activation of VMH, DMH, PVN (557), posterior (PH) and supra-optic hypothalamic nuclei (85) in response to trigeminovascular stimulation, and descending projections exist from the PVN, PH, perifornical, A11 and retrochiasmatic area (1, 688), to the TCC. Projections from the PH (78) and PVN (688) are known to modulate basal and nociceptive meningeal-evoked activity of trigeminal neurons. These connections are thought to contribute to migraine symptoms such as loss of appetite and pain modulation. The VMH also sends topographically organized projections to areas involved in nociceptive modulation such as the PAG, LC, parabrachial nucleus and NTS (145) and the PVN sends descending projections to the superior salivatory nucleus (688). It is clear that various hypothalamic nuclei are ideally positioned to mediate the integration of the trigeminovascular system with dietary fluctuations including disrupted feeding patterns.

The NTS is known to be involved in pain modulation, and is activated in response to dural nociceptive trigeminovascular activation, a response inhibited by triptans (421). A region seen activated on human brain imaging in the premonitory phase of migraine would be consistent

with NTS activation (560). Given that descending mechanisms from midbrain structures have been hypothesized to contribute to the triggering of migraine, altered feeding, such as fasting or hypoglycemia, which affects neuronal firing in the NTS could alter the descending modulation of trigeminovascular neurons, as well as alter appetite during migraine. Furthermore, the NTS is intrinsically involved in the 'emetic reflex arc' (602). Consistent with that involvement, medial-caudal NTS neurons are activated in cat (463) and monkey (330, 422) when dural afferents are stimulated. Remarkably, vomiting is a common symptom of migraine that can often ameliorate, or even stop an attack (152). It is possible to speculate that NTS activation might be part of the adaptive processes that take place in the brain before and during an attack, as a consequence of the migraine.

The VTA is also involved in nociceptive processing (34, 64, 230, 698), food reward, drug addiction (479, 600), and mood disorders (697). Food cravings and alterations of mood are considered by some patients to be present in the premonitory phase of the migraine attack (228, 300) and, importantly, the VTA was shown to be active during the premonitory phase (559).

In order to control body fuels during and after periods of fasting, several adaptive mechanisms take place, including reduction of resting metabolic rate and blood glucose, the priority of gluconeogenesis over glycogenolysis, and the production of ketones. These adaptations are caused or followed by several hormonal changes, including the decline in insulin and leptin serum levels and the rise in glucagon, catecholamines and cortisol (140, 214, 263, 478, 707).

Anatomically, there is increased activation of the perifornical region, DMH, VMH and arcuate hypothalamic neurons, which include activation of orexin-containing neurons (214), and elevation of mRNA levels of orexin and melanin-concentrating hormone (MCH) (672, 701). Furthermore NPY levels in the arcuate nucleus and PVN increase in response to food deprivation or food restriction and normalize after refeeding (118, 144, 647, 699), and NPY release in the PVN increases before a programmed meal and decreases during the course of the meal (455). Also, hypoglycemia induced by insulin causes significant activation in the PVN, as well as the LC, dorsal motor nucleus of the vagus and NTS (873).

ii. Feeding peptides and migraine

Considered altogether the data are consistent with a view that blood glucose fluctuations, as a consequence of changes to orexigenic and anorexigenic neuropeptides in specific hypothalamic nuclei, may increase the predisposition to triggering migraine through altered feeding, or reflect a change in that predisposition. Two studies demonstrate consistently higher insulin levels in migraineurs compared to controls (148, 676) suggesting that insulin resistance may be present in migraineurs. A significant prevalence of insulin resistance was also observed in chronic migraine patients (261). A significant association between a polymorphism of five single nucleotides of the gene encoding for insulin receptors in migraineurs has been found (590), which may affect insulin resistance during fasting in migraineurs. Thus, migraine might be more likely in susceptible persons when there is low insulin receptor activation (590), through fasting. It is interesting that mild hyperinsulaemia is reported in NPY Y_1 receptor deficient mice (489),

which might imply that low NPY Y_1 receptor activation impairs glucose and insulin metabolism that is reported in migraineurs. Furthermore, while obesity is not considered a risk factor for migraine, it is associated with an increase in frequency and intensity of attacks (99, 102, 858). Plasma OxA levels correlate negatively and plasma leptin levels correlate positively with body mass index (BMI) (5), therefore, obese individuals should present lower plasma OxA levels and higher plasma leptin levels when compared to normal individuals. This is in accordance with the lower peripheral OxA levels seen in episodic migraineurs (146) and, also, with higher blood leptin levels shown in non-obese female migraineurs (90), compared to healthy controls. In some respects disentangling cause and effect remains the major challenge in terms of meal skipping.

Looking at the wider impact of hunger, it is a strong and basic physiological drive. It involves activation of several pathways, including the hypothalamic orexinergic system, and is the product of multiple perceptions (taste, smell, sight, thoughts, visceral) and motivations. While migraine clearly includes pain, it has also been described as an altered activation (or perception of activation) of the senses, senses that are affected by hunger, including the trigeminovascular system. We can look at this in two ways in susceptible migraineurs; first, hunger triggers changes in activation in feeding centers in the brain, aimed at promoting feeding, which affect our sensory system, altering our perception of sensory inputs, which includes noxious craniovascular somatosensory inputs, but also those of sound, vision and smell, amongst others. Secondly, it could be argued that alterations in the individual perception of hunger, might in itself also cause disturbances of somatosensory processing, especially nociceptive

processing that result in migraine head pain. Thirdly, and perhaps more likely, there is a global alteration in the perception of our motivations and senses, including hunger and nociception, which become symptoms of the same cause and trigger, and thus all these symptoms of migraine are essentially a consequence of a brain state, rather than a single trigger.

B. 'Sleep disruption'

The relationship between migraine and sleep has been debated for a number of years (625): sleep is considered an effective means of alleviating pain associated with migraine; migraine can emerge during nocturnal sleep or following a brief period of daytime sleep; attacks can be preceded by a lack of sleep. Furthermore, sleepiness might also emerge during various phases of a migraine attack (71). Sleep deprivation, or consistent interrupted or reduced sleep is also described by many patients as a possible trigger of migraine (107). The regulation of sleep, particularly within the hypothalamus, is strongly linked to the regulation of feeding processes, and the interaction of both of these homeostatic mechanisms is likely involved in the triggering of migraine.

1. Anatomy of sleep

Both sleep and feeding rhythms are synchronized to the environmental 24-h cycle mainly by light–dark information perceived by the eyes, and regulated within the hypothalamus. Generation of these rhythms occurs in the master circadian clock, the suprachiasmatic nucleus (SCN) of the anterior hypothalamus (201, 867). The SCN output is crucial for synchronization of

many metabolic and endocrine factors, such as glucose (143, 491, 693)and leptin (456). Zurak (883) reviewed the role of SCN in migraine and suggested that dysfunction of the SCN could be related to the prodromal phase of a migraine attack, suggesting SCN as the initial site of migraine attacks.

Feeding behavior and metabolite availability can in turn regulate the circadian clock. The DMH, a suggested food entrainable oscillator (354), receives neural input from feeding control areas (790) and is a major target of the SCN (838). DMH also projects to brain regions critical for the regulation of sleep and wakefulness (167). Specifically, DMH sends GABAergic projections to the sleep-promoting ventrolateral preoptic nucleus (VLPO) (548), and glutamate-thyrotropin-releasing hormone projections to the wake-promoting LH area (167). Therefore, increased neuronal activity in the DMH might promote wakefulness by simultaneously inhibiting sleep-promoting neurons in the VLPO and activating wake-promoting neurons in the lateral hypothalamus. The DMH also sends a dense projection to the PVN (255, 789). The activation of these pathways might explain why lack of sleep or wakefulness might trigger a migraine headache attack as Fos protein expression has been demonstrated in the DMH and PVN in an experimental model of migraine in animals (557); and PVN neurons directly control both spontaneous and evoked activities of spinal TCC neurons (688).

Midbrain nuclei, already described with respect to mechanisms that control pain, may also be involved in the triggering of migraine, as well as contributing to the associated symptoms via projections to hypothalamic and other brainstem and diencephalic nuclei. As well as controlling

pain modulation, ‘ON’ and ‘OFF’ cells in the RVM and NRM are also involved in controlling responses to external innocuous stimuli, motor activity and homeostatic processes (571, 573). ‘ON’ cells are state-dependently active during waking hours, but not during feeding and micturition, or during sleeping (65, 278, 279, 525). Whereas ‘OFF’ cells are active during sleep, and active during waking only prior to micturition as well as during feeding. Therefore ‘OFF’ cell firing in these midbrain structures, during important homeostatic functions such as sleep, feeding and urination prevents responding to innocuous and even acute noxious stimuli, whereas during waking ‘ON’ cell firing facilitates alertness to sensory stimuli. Furthermore, the vlPAG participates in mechanisms of arousal, through the activation of dopaminergic neurons during wakefulness and inactivation of these neurons during sleep (549); and vlPAG is also involved in the switch between non-REM and REM sleep (286, 550). These important mechanisms probably represent important evolutionary developments to control sensory, autonomic and motor processes during different levels of alertness to provide the greatest protection to the animal from nociceptive inputs. Certainly in the context of potential migraine triggers, sleep deprivation is a homeostatic process that results in specific neuronal responses in the PAG-RVM pathway, particularly ‘ON’ cell activation and inhibition of ‘OFF’ cell firing. In migraineurs, it is possible that altered responses of ‘ON’ and ‘OFF’ cells to nociceptive and homeostatic changes, such as sleep disruption, and the neuronal projections of the PAG-RVM systems to hypothalamic nuclei and spinal and trigeminal nociceptive neurons, described above, contributes to triggering the sensory and physiological symptoms of migraine.

2. Neurochemicals in sleep regulation

Interestingly, sleep is affected by feeding, specifically endogenous energy reserves, which may impact its influence as a migraine trigger. Indeed sleep is thought to be dependent on the availability of utilizable metabolites at the cellular level (198). Sleep debt has been shown to have a harmful impact on carbohydrate metabolism and endocrine function (747). Indeed, sleep deprivation, induces an increase in glucose and insulin plasmatic levels (684) and lower glucose tolerance (747) in humans. Furthermore, melanin-concentrating hormone (MCH) is known to promote sleep (6, 824) and integrates energy homeostasis responses (722). Increased extracellular glucose levels are known to enhance the electrical excitability of these neurons (125), and thus, the excitatory actions of glucose on MCH neurons may promote rest and, conversely, a fall in glucose levels would decrease the excitability of MCH neurons, hence suppressing sleepiness (125). Collectively, these data might support the view of an impairment of glucose metabolism that has already been proposed in migraine patients (148, 676).

i. Hypoglycemia and arousal

Recent evidence indicates that hypoglycemia produces arousal from sleep in normal adult humans (68, 288). Several neuropeptides involved in food regulation are known to also influence sleep regulation and consciousness. Hypothalamic orexin levels are highest during wakefulness and lowest during sleep (258, 469), with almost total cessation during REM periods, *in vivo* (521). It is known hypoglycemia in rats strongly activates wake-promoting orexin neurons (141, 611, 651). Furthermore, insulin-induced hypoglycemia activates orexinergic and cholinergic neurons, increasing arousal in adult male rats, similar to the effect

of nocturnal hypoglycemia in adult humans (793). Thus, orexins appear to stimulate feeding and increase metabolism (774) during active, awake periods. It has been reported that deficiency in orexin neurotransmission results in the sleep disorder narcolepsy in mice, dogs, and humans (161, 532, 628, 778) and one aspect of orexin activity is the direct excitation of noradrenergic neurons in the LC to promote wakefulness (117, 416). These observations are important as clinical studies demonstrate that patients with narcolepsy show a higher prevalence of migraine (195) and that migraine attacks initiate mostly in the early morning hours (33, 399).

ii. Orexins, feeding and sleep

Another feature that connects orexins with feeding and sleep is the hunger-induced wakefulness, a well-established phenomenon in animals (112, 443), wherein food deprivation induces expression of Fos protein in orexin neurons and increases mRNA orexin levels (214), but food deprivation does not induce wakefulness in orexin-deficient mice (865). This is consistent with electrophysiological findings showing that food deprivation induces synaptic changes in orexin neurons, where the number of asymmetric (putative excitatory), but not symmetric (putative inhibitory), synapses on orexin-containing cell bodies are elevated significantly in mice after just one episode of food deprivation, compared with fed controls (415). From an adaptive evolutionary perspective, synaptic plasticity in orexin neurons may be a critical mechanism contributing to the determination of behavioral status by energy status in animals.

iii. Sleep and NPY

Arcuate *POMC* neurons and *NPY/AgRP* neurons are also involved in sleep regulation (432, 476, 522). Bilateral destruction of NPY receptor-expressing neurons in the arcuate nucleus (847) are required for integration of sleep-wake rhythms. In humans, NPY enhances sleep by prolonging the sleep period and reducing sleep latency and wakefulness (51, 390). However, studies in rats show that NPY has opposing effects on sleep patterns depending on the site of administration (752, 776, 796).

iv. Sleep, leptin and body mass

While sleep can be affected by changes in energy homeostasis, changes in sleep patterns can likewise disturb endocrine regulation of energy homeostasis (475). Leptin plasma levels show a diurnal variation, with levels increasing during nocturnal sleep in humans (738, 841). Leptin also influences sleep stages, as systemic leptin significantly decreased the duration of REM sleep and increased the duration of slow wave sleep in rats (739). Furthermore, studies in humans show lower leptin levels during short habitual sleep time (154, 618, 746, 777), suggesting that sleep restriction causes increases of appetite and higher BMI. Recent epidemiological studies have pointed to a distinct relationship between sleep duration and body weight, suggesting a U-shaped association in that both shortened and extended sleep durations coincide with increases in body weight (290, 380, 777, 826). These effects might be important in the context

of migraine, as metabolic syndrome has been suggested to explain obesity as a risk factor for migraine frequency and severity, as well as to progression from episodic to chronic migraine (99, 101).

v. Sleep disturbance- trigger or consequence

While it is still not clear whether disruption to homeostatic regulation is actually a trigger of migraine, a symptom, or contributes to both, changes of appetite (loss of appetite or hunger), sleepiness and irritability reported during migraine may be mediated by reciprocal projections between nociceptive trigeminovascular neurons and the lateral hypothalamus. In this area neurons expressing MCH or orexin regulate food and water intake, sleep and arousal, through widespread projections to the cerebral cortex, brainstem and spinal cord (104, 701, 814). It could be argued that there is a hyperactivity of the brain mechanisms responsible for the hunger behavior in the premonitory phase of migraine, leading to arousal and lack of sleep. Hence, in some cases it would not be the voluntary bedtime sleep deprivation that would trigger the headache attack but, instead, an endogenous wakefulness mechanism that would be active, or a perception of wakefulness state, that could trigger the activation of the trigeminovascular system. Sleep deprivation is also known to activate hypothalamic feeding mechanisms and, thus, not only trigeminovascular neuronal pathways would be activated through reciprocal projections between the TCC and the hypothalamus, but also changes of appetite would be likely to happen. Therefore, in some respects, it may be difficult to dissect a difference between the mechanisms triggered by food or sleep deprivation, but it is clear each

can affect the other, and may increase the likelihood of a migraine attack.

C. ‘Stress’

Stress and negative emotions are commonly listed as triggers by migraineurs (227, 300). Although stress-sensitive patients may perceive more stress in the days before an impending migraine attack, there is very little experimental evidence showing a biological stress response in migraineurs. Migraine patients were reported to have large variations in plasma cortisol levels, a stress response indicator, when compared to the control group, and a subgroup of migraine patients exhibited abnormal circadian levels of cortisol (882). A study also showed statistically significant associations between the cortisol response and both headache severity and duration (355). While stress as a trigger may also be related to other potential triggers that are a response to disrupted homeostasis, such as sleep and food deprivation reviewed above, we will describe the mechanisms through which ‘stress’ may contribute to these processes.

The hypothalamo-pituitary-adrenocortical (HPA) axis is recruited by the organism in response to real or perceived threats to homeostasis or ‘stress’. Corticotropin-releasing hormone (CRH) and vasopressin (AVP) are produced in the parvocellular neurons of the hypothalamic PVN. These neurons secrete peptides into the portal vessel system to activate the synthesis of pro-opiomelanocortin (POMC) in the anterior pituitary, which is processed to corticotropin (ACTH), opioid and melanocortin peptides, among others. Then, ACTH stimulates the adrenal cortex to secrete cortisol (humans) and corticosterone (humans, rats and mice) as a stress response (reviewed in 205). Signals of homeostatic imbalance in the brainstem also lead to activation of

the HPA axis:ascending brainstem and spinal pathways project to the parvocellular divisions of the PVN. For instance, noradrenergic and adrenergic projections to the hypophysiotrophic zone of the PVN originate in the NTS and C1-C3 (189, 190) and participate in the HPA axis. Furthermore, in a preclinical animal model of migraine using nociceptive activation of trigeminovascular neurons, a stress protocol in these animal reduced the ability of PVN neurons to provide descending control of trigeminovascular nociceptive neurons (688).

1. Neuropeptides in stress

Similar to feeding and sleep, stress is also influenced by the orexinergic system; orexin mRNA is increased in the LH due to stress (436). In patients with chronic headache and medication overuse headache (MOH), increased cerebrospinal fluid levels of corticotrophin-releasing factor and OxA have been demonstrated (706). These results are in agreement with a suggested hypothalamic–pituitary axis alteration in these patients (675).

2. Orexins and corticosteroids

In preclinical studies, ICV administration of orexins in the rat produces activation of parvocellular PVN neurons that are putative CRH-containing neurons (200, 244, 488). Central injection of orexins also caused significant secretion of ACTH (488) and elevation of plasma concentration of corticosterone (244, 436, 446, 488), and this response is completely eliminated by pre-administration of the CRH antagonist, α-helical CRH9-41 (446). The CRH-producing neurons in the parvocellular PVN also show abundant expression of the OX_2R gene,

as well as receiving axonal projections from orexin-producing neurons (200). Recent experimental data in this regard indicate that the CRH peptidergic system directly innervates and can depolarize orexin-expressing neurons, an effect which is blocked by a CRF-R1 antagonist. In addition, activation of orexinergic neurons induced by high arousal states, including stress, is impaired in CRF-R1 knockout mice (257, 856, 857). These data suggest that the CRF-R1 receptor mediates stress-induced activation of the orexinergic system (706). There are also experimental findings suggesting that orexins in the CNS may be involved in the activation of central CRH neurons induced by stress (436). Furthermore, it is suggested that CRH activates the orexin system, relaying orexin-A to brainstem nuclei such as the LC as well as the nucleus accumbens, VTA and amygdala (856), which are critical structures involved in determining the rewarding or aversive value of an environmental stimulus such as stress (reviewed in 697).

3. Leptin and corticosteroids

It is possible that orexins together with leptin may take part in counter-regulatory mechanisms, which, through the modulation of glucocorticoid secretion, are involved in the maintenance of physiological blood glucose levels and energy homeostasis. Indeed, as opposed to orexin-induced glucocorticoid secretion, leptin has been shown to inhibit the stress-induced activation of the HPA axis (388) and to inhibit glucocorticoid secretion (113, 301, 302, 669). Individuals who have perceived psychological stress (self-reported) had higher leptin levels, compared to those patients who reported little stress in their daily life (646). Since the central orexin system is related to physiological stress responses and activation of both orexin receptors modulates

acute dural and facial nociceptive inputs, it is likely that there is a causal link between a stress response, the potential origin of the premonitory symptoms of migraine and the descending modulation of trigeminovascular nociceptive traffic.

4. Neuropeptide Y (NPY)

NPY is an established moderator of stress responses (reviewed in 387, 744, 792), by mediating activation of the HPA axis. It has been shown that NPY-containing neurons form a prominent afferent pathway between the arcuate nucleus and the PVN (529, 534). In addition, half of the glucocorticoid receptor (GR)-positive neurons in the arcuate nucleus are also immunoreactive for NPY (392). Inadequate nutritional intake, such as food deprivation/fasting also activates the HPA axis, demonstrated by increased cortisol release in humans (87, 818) and increased activity of NPY neurons in animals (229, 377). Intra-PVN administration of NPY stimulates food intake and this effect is suppressed by CRH (389). Furthermore, NPY release in the PVN modulates activity of parvocellular neurons and increases ACTH and corticosterone release (32, 437). This activation seems to be explained by the presence of NPY Y_1 receptors on CRH neurons in the PVN (222), and NPY Y_5 receptors may also be involved in regulating HPA axis function in rats (454). Functional NPY gene variation has been proven to influence the behavioral adaptation to stress (533) and as described above, NPY is able to modulate acute dural nociceptive inputs in the TCC by inhibiting neuronal firing through the activation of the NPY Y_1 receptor (570). Thus it is possible that impaired central NPY signaling might be involved in stress-induced migraine.

5. Stress and migraine

It is assumed that, in general, acute stress should not result in detrimental effects. Instead, through physiological adaptation, the organism should become capable of functioning in the midst of this altered environment. However, we have detailed above how migraineurs seem to be particularly susceptible to environmental changes. They might therefore have enhanced neuroendocrine responses, as a manifestation of enhanced sensitivity of brainstem and diencephalic pathways, leading to inappropriate processing or interpretation of stressful information. The parvocellular division of the PVN seems most likely to play a central role in the homeostatic stress response and these neurons are known to project to the brainstem and spinal cord (775) and more specifically to regions of the TCC (688). In addition, afferent pathways such as limbic pathways that are activated by psychological stressors (444), and ascending brainstem pathways that convey visceral and sensory stimuli may also activate CRH neurons in the PVN (687). Therefore, activation of parvocellular neurons in the PVN might be key to the cascade of events leading to the activation of the trigeminovascular system and, ultimately, could explain the low stress resilience in susceptible individuals or the stress-induced migraine.

XI. Pharmacology of Migraine – Treatments

Activation of the trigeminovascular system results in the release of a number of neuropeptides based upon the sympathetic, parasympathetic and sensory innervations of the cranial vasculature, summarized in Table 2. The sympathetic innervation is characterized by NPY and noradrenaline (239-241), both of which are vasoconstrictors while the parasympathetic fibers

are characterized by VIP and PACAP, which are amongst the most potent vasodilators (240). The sensory innervations are characterized by substance P, CGRP and PACAP (247). Experimental activation of the trigeminal ganglia in animals and humans (324) results in the release of SP and CGRP which can be inhibited by different triptans. Given the release of SP and at the time, an emerging theory of a role for neurogenic inflammation in the pathophysiology of migraine, an unsuccessful program targeting the neurokinin 1 receptor ensued (583). The failure of substance P directed interventions was highlighted in follow up studies exploring neuropeptide changes in migraine and targeted cerebrovascular stimulation in animals. In these studies CGRP, VIP and PACAP are most commonly upregulated with no change in substance P levels (325, 874). A summary of approaches in, or near development, for the treatment of migraine is found in Table 4.

A. Serotonin (5-HT)

The initial involvement of serotonin (5-HT) in migraine was postulated more than 50 years ago with seminal observations of increased 5-hydroxyindoleacetic acid (metabolite of 5-HT) associated with migraine attacks (191, 734). Further evidence was gained from two key studies identifying reductions in platelet 5-HT during attack onset (50) and that infusion of 5-HT could abort both reserpine-induced (468) and spontaneous headache (503). In response to these seminal studies the 5-HT receptor system gained much attention culminating in the discovery of the triptans, serotonin, $5\text{-HT}_{1B/1D}$ receptor agonists (434).

1. Triptans- Serotonin, 5-HT$_{1B/1D}$ receptor agonists

Of the fourteen 5-HT receptors identified all except 5-HT$_3$ (ligand-gated ion channel) are G protein-coupled receptors (430). While the triptans are classed as 5-HT$_{1B/1D}$ receptor agonists, most also activate to a lesser extent the 5-HT$_{1A}$, 5-HT$_{1E}$ or 5-HT$_{1F}$ receptors (310, 434). Originally the triptans were developed to act on the craniovasculature, an idea supported by their clear vasoconstrictive actions (174, 177, 264, 265) and the preferential expression of the 5-HT$_{1B}$ receptor on cranial rather than peripheral vessels (809). In conjunction with progress in theories of migraine (section XI), understanding of the mechanism of action of the triptans has evolved, largely due to the discovery that triptans are not selective cerebral vasoconstrictors and the presence of central effects. Both sumatriptan and dihydroergotamine, a less specific 5-HT$_{1B/1D}$ receptor agonist (86), were demonstrated to inhibit trigeminal afferents by an exclusively neural mechanism, without effect of vessels, that is also acting on central trigeminal neurons (419, 420, 462). A neural mechanism of triptans on peripheral trigeminal nerve endings could inhibit proinflammatory neuropeptide release and neurogenic dural vasodilation (853, 854), which was consistent with the developing theme of migraine as a neurovascular disease.

It is now clear that the triptans may be acting within the TCC to modulate trigeminovascular nociceptive neurons which express 5-HT$_{1D}$ and 5-HT$_{1F}$ receptors (170, 426, 552). It has been demonstrated that TCC neuronal activity can be inhibited by more centrally active triptans (314, 322, 331, 333, 334) and this effect is mediated predominantly by 5-HT$_{1B/1D}$ receptors (332). The growing interest in possible CNS sites of action for the triptans led to more focused approaches relying upon direct delivery to discrete areas combined with detailed electrophysiological

approaches. Microiontophoresis of 5-$HT_{1B/1D}$ agonists on trigeminovascular neurons in the TCC results in a clear reversible inhibition of trigeminal activity (763), highlighting this key relay center as a major site of action. However, as discussed earlier, multiple CNS sites of action have now been established including the PAG (77), PVN (688) and thalamus (730). The diversity of the target sites raises an intriguing scenario where modulation of 5-$HT_{1B/1D}$ receptors could influence ascending trigeminothalamic projections in tandem with actions on descending pain modulatory structures.

2. Ditans- Serotonin, 5-HT_{1F} receptor agonists

Despite the clear pharmacology of the triptans in the treatment of migraine their use is limited in patients with cardiac risk factors (223), resulting in the need to target receptors lacking vasoconstrictive actions. One such target is the 5-HT_{1F} receptor which is activated to a degree by some triptans, such as naratriptan, and not by others, such as rizatriptan (310). 5-HT_{1F} receptors are found in the TCC and trigeminal ganglion (42, 115, 124, 170), and their activation inhibits trigeminal activity in the rat and cat (728, 762). Indeed it can be shown that after blockade of 5-HT_{1B} and 5-HT_{1D} receptors with SB224289 (724) and BRL-15572 (670), respectively, naratriptan retains an inhibitory effect on trigeminocervical responses evoked from superior sagittal sinus (316), while a 5-HT_{1F} receptor agonist LY344864 (663) has inhibitory TCC effects and no effect on the cat carotid circulation (316). Moreover, the inhibitory effect of alniditan, a 5-$HT_{1B/1D}$ receptor agonist with no 5-HT_{1F} effects (528) and proven anti-migraine effects (352), is completely blocked by the combination of SB224289 and BRL-15572 (316). Evidence for a neural mechanism which may be devoid of vascular effects (114) is further

supported by selective 5-HT_{1F} inhibition of dural extravasation and inhibition of TCC neuronal activation following trigeminovascular activation (449, 604, 605, 624, 663). While the development of specific 5-HT_{1F} receptor agonists has not been without complication (350), successful phase II randomized clinical trials with lasmiditan (624) highlight the potential of targeting specific neuronal targets (260, 267).

B. Calcitonin gene-related peptide (CGRP)

CGRP is a 37 amino acid neuropeptide with potent vasodilator effects (486, 852) that is produced by alternative splicing of the calcitonin gene (35, 692). Other members of the gene family are amylin, adrenomedullin and adrenomedullin 2 (intermedin) (694). With respect to the nervous system αCGRP is predominantly expressed, while βCGRP is associated with the enteric sensory system (617). CGRP acts at two receptors, one the so-called canonical CGRP-receptor complex is made up of a G-protein-coupled receptor consisting of a seven transmembrane spanning protein (calcitonin receptor-like receptor; CLR) and a single transmembrane receptor modifying protein (RAMP) 1 (16, 593). RAMP 1 is critical for the transport and cell surface expression of the CGRP receptor complex (593) and its overexpression results in migraine like phenotypes including light aversion and CGRP induced allodynia (453, 680, 681, 696). The second CGRP receptor has been called the amylin receptor (AMY_1) and consists of the calcitonin receptor (CTR) and RAMP 1 (382). It has now been clearly shown that CGRP activates this receptor (831). Amylin is a glucoregulatory hormone and has additional bone metabolism effects.

CGRP is widely distributed including in the striatum, amygdale, hypothalamus, thalamus, brainstem and TCC (404, 816, 868). Within the primary afferent trigeminovascular pathways CGRP expression is highest in the sensory trigeminal ganglion and its Aδ and C-fiber projections to cerebral and dural blood vessels as well as centrally to the spinal cord (242, 246, 780), where it can impact second order ascending projections. Functional CGRP receptors and binding sites have been identified on dural artery smooth muscle cells and in the trigeminal ganglia, thalamus, hypothalamus, amygdale, cortex and brainstem (238, 246, 523, 643, 769). Interestingly in the TCC CGRP receptors are thought to co-localise with CGRP in terminals of primary afferents and not ascending fibers (523).

CGRP is a potent vasodilator which when given to migraine sufferers is known to trigger attacks (508); however, the exact triggering mechanism is not clear since VIP another potent vasodilator fails to initiate attacks (674) suggesting a non-vascular mechanism. As discussed earlier CGRP is released during spontaneous (325) or triggered attacks (289), which can be inhibited by triptan treatment (323). Experimental activation of trigeminal ganglion cells is known to result in the release of CGRP, which is dose dependently inhibited by 5-HT_{1B1D} agonists (231), highlighting the trigeminal ganglion as a key site that may be a target of CGRP receptor antagonism and triptan response (245, 247). In addition to its vascular effects, CGRP has emerged as a key modulator of neuronal function which has important effects on neurotransmitter systems such as the glutamatergic system (760). Local administration of CGRP facilitates dorsal horn and TCC nociceptive neurons, while CGRP antagonism points towards a

tonic facilitatory role as blockade with the truncated $CGRP_{8-37}$ reduced neuronal responses below baseline levels (760). Similarly targeted administration of CGRP to the ventrolateral PAG facilitates trigeminovascular processing via descending modulatory mechanisms (668), while thalamic modulation identified a clear inhibitory action of CGRP antagonism, both on nociceptive signaling and spontaneous background activity (769).

1. Gepants- CGRP receptor antagonists

Based on the available bench and clinical data (395), an effort was commenced to develop CGRP receptor antagonists (226). Olcegepant (BIBN4096BS) demonstrated excellent efficacy in animal models of CGRP-induced vasodilation (610), and interestingly reversed spinal morphine tolerance (667). In a proof-of-principle phase II study using an Up/Down design rule, it was effective at a dose of 2mg intravenously (638). It was never commercialized due to formulation issues. Subsequently telgecepant (MK-0974) also demonstrated efficacy in better than placebo and comparable to triptans (179, 393, 396), as the first oral CGRP receptor antagonist. It had excellent long term tolerability (178), and was also well tolerated in patients being investigated for coronary artery disease (397). However, the development of telcagepant and its follow-on MK-3207 (391) was halted when liver enzyme problems emerged in a preventive study, which was interestingly enough positive (394). It has been generally considered as an off-target effect of a metabolite of the compounds, which has not been reported with rimagepant (562) or BI44370 TA (216). Most recently a further compound ubrogepant has been identified, again it was effective in a placebo-controlled trial as an acute migraine treatment (828), and along with

AGN-241689, which will be developed as a preventive (Table 4), this class of therapies has much promise.

2. CGRP peptide and receptor monoclonal antibodies (-numab & -nezumabs)

In order to capitalize on the proven anti-migraine effects of blocking CGRP mechanisms in migraine, monoclonal antibodies have been developed as novel preventive treatments.Three antibodies to the CGRP peptide, ALD-403 (224), galcanezumab (LY2951742, 225) and TEV-48125 (96), have each published a positive randomized, placebo-controlled trial in episodic migraine prevention that has been positive. One CGRP ligand monoclonal antibody has published positive data for chronic migraine (97), and the CGRP receptor (CLR/RAMP1 complex) antibody, erenumab, has also presented positive placebo-controlled trial data in episodic migraine (770). These antibodies seem well tolerated with no significant adverse events across the studies, and no issues emerging from phase I studies (98, 103, 204). These compounds represent a truly innovative, immunopharmacological approach to blocking CGRP mechanisms that is now in phase III development.

C. Nitric Oxide Synthase

Nitric oxide (NO) is an abundant gaseous signaling molecule which like the previously mentioned neuropeptides is involved in a variety of functions including endothelial dependent vasodilation (441). Nitric oxide donors, such as glyceryltrinitrate/nitroglycerin, like CGRP (508) and PACAP (720), are used for the experimental induction of migraines (439, 441) and

premonitory symptoms (11). Given the clear role of NO donors in triggering attacks it is unsurprising that they have received similar attention in preclinical models where they produce vasodilation (30, 767) and trigeminovascular activation (480, 495, 783). Perhaps the most interesting feature of experimental NO use is the biphasic nature of the TCC activation with an initial acute activation and a delayed general activation (20, 480) which appears to mirror the acute throbbing and delayed migraine seen in patients. NO donors clearly facilitate trigeminovascular activation resulting in activation of the TCC with resultant increases in CGRP and neuronal nitric oxide synthase (nNOS)(652, 653) and NOS inhibitors have also proven preclinical efficacy. Nitric oxide synthases are a family of enzymes which catalyze the production of NO consisting of endothelial (eNOS), neuronal (nNOS) and inducible (iNOS). Non-specific blockade of NOS prevents neurogenic dural vasodilation (31) and TCC neuronal activation (417, 634). Interestingly and in support of the current theme of migraine as a neurovascular disorder specific nNOS inhibitors mimic the effects of non-specific blockers (31, 93).

The available clinical and preclinical data highlighted NOS inhibitors as a reasonable target for anti-migraine therapy and while early studies showed beneficial outcomes (507) they were not without issue. Given the unwanted side effects of eNOS actions current research has focused towards other specific NOS inhibitors, with the initial study of a specific iNOS inhibitor failing to reach its clinical end point in both an acute (649) and preventive study (403). A mixed triptan and nNOS inhibitor NXN-188 was also found to be ineffective in both migraine without aura

(595) and specifically in the aura phase (428). The issue of a possible effect of a specific nNOS inhibitor is unresolved.

D. Pituitary adenylate cyclase-activating peptide (PACAP)

PACAP like CGRP is released during migraine (803, 874, 875) and can trigger attacks (720) in patients leading to its exploration as a possible anti-migraine target. It is a member of the VIP-glucagon growth hormone releasing factor-secretin superfamily which comes in two forms; PACAP-38 accounts for approximately 90%, whereas PACAP-27 is relatively poorly expressed (57). Like the majority of neuropeptides targets PACAP is widespread throughout the CNS and peripheral tissue (574, 806, 808) where it has potent vasodilator effects. PACAP is known to have a specific uptake mechanism into the brain (70). The pharmacology of PACAP is slightly more complex due to its binding affinities to three G-protein coupled receptors which also bind VIP. It should be highlighted again that VIP does not induce migraine unlike PACAP and CGRP, highlighting the importance of non-vascular targets. VPAC1 and 2 bind VIP, PACAP-38 and PACAP-27 in order of descending affinity while PAC1 is relatively specific for PACAP (492). It is expressed in the TCC, spinal cord, trigeminal ganglia, sphenopalatine ganglia and CNS structures including the thalamus, hypothalamus and brainstem (186, 450, 574, 779, 808). It is likely the central expression pattern underlies the proposed role in migraine, and like CGRP, PACAP has been linked to sensitization and light aversion (564). This facilitatory role has recently been demonstrated in the hypothalamus where PACAP administration facilitated trigeminovascular nociception via a PAC1 mechanism (688).

Recently, in a rodent model of nociceptive trigeminovascular activation it has been shown that VIP and PACAP-38 caused short-lived meningeal vasodilation mediated by VPAC2 receptors, without activation of central trigeminovascular neurons (17). PACAP-38 and not VIP caused a delayed activation and sensitization of central trigeminovascular neurons. In this context behaving as it does in triggering migraine (720). Intravenous delivery of a PAC1 receptor antagonist inhibited the peripheral meningeal vasodilatory effects of dural trigeminovascular nociception, whereas only central (intracerebroventricular) administration of the PAC1 receptor antagonist inhibited dural nociceptive trigeminovascular activation (17), suggesting a central PAC1 receptor as an important target. While not as advanced as CGRP targeting, it is clear that PACAP has a role to play in the pathogenesis of migraine and as such will continue to progress as a therapeutic target.

XII. Theories of migraine

Theories of migraine have changed greatly over the years, often turning full circle and returning to the original theories from 250 years ago. However the last 60-70 years has seen the largest development of theories as a consequence of medical research and advancing scientific technologies. Certainly since the observations of Harold Wolff and colleagues in the 1940s, where mechanical stimulation and distension of cranial blood vessels resulting in headache-type pain in patients undergoing cranial surgery, a '*vascular theory of migraine*' took on momentum. The theory is driven by the idea that vasodilation of extracranial arteries and also intracranial blood vessels produce mechanical activation of perivascular nerve fibers that

innervate the vessels, resulting in headache pain (861). This concept was supported by the observation that migraine headache commonly has a pulsating quality, as well as by more recent studies showing that nitric oxide and CGRP are able to trigger migraine attacks and the vasoconstrictive and therapeutic effect of triptans support this. However, recent preclinical and clinical data in these same areas demonstrate that this concept was based on misinterpretations. In contrast to the common assumption, the experienced pulsations during a migraine attack are not synchronized with cardiac contractions as the painful pulsations have a lower frequency (14, 603). Furthermore, arterial vasodilation produced by VIP does not trigger migraine headache in patients (674) and arterial vasodilation that has been reported during CGRP-evoked migraine (58) is modest and unlikely to be sufficient to activate perivascular nociceptive afferents. In addition, Amin and colleagues (40) demonstrated in a study using state-of-the-art MR-angiography techniques that meningeal vessels do not dilate during spontaneous migraine attacks (40), something which has been previously demonstrated during experimentally triggered migraine (713). The results further indicate that intracranial vessels show only a slight dilation that is not affected by sumatriptan, making the vascular theory obsolete (40).

The importance of the intracranial vasculature, or its nerve fiber innervation, still remains significant. The studies of Ray and Wolff demonstrated that headache-like pain and nausea can be generated by stimulation of the dura mater, particularly surrounding the dural and cerebral blood vessels, whereas stimulation away from the vessels was not effective at inducing pain (679). As described above the dural blood vessels are richly innervated by nociceptive

unmyelinated (C-fiber) and myelinated (Aδ-fiber) axons that originate in the trigeminal ganglion, and contain vasoactive neuropeptides (Table 2). These data consolidate the theory that headache in migraine may be mediated by activation of nociceptive nerve fibers that innervate the meningeal blood vessels. The key question is what causes these fibers to become activated during migraine. One proposal in the 1980s was that a '*sterile neurogenic inflammation*' of the dural meninges may result in activating the perivascular innervation to trigger migraine (612). Activation is driven by local dural release of endogenous inflammatory mediators such as CGRP, substance P, neurokinin A and prostaglandins, which increase local blood flow (predominately driven by CGRP), leakage of plasma proteins from blood vessels, mast cell degranulation and platelet aggregation. It is induced experimentally in rats by trigeminal ganglion stimulation, a process that also induces similar responses in the retina (565, 566). The success of acute migraine treatments including ergot alkaloids, sumatriptan and non-steroidal anti-inflammatory drugs in blocking these effects (138, 139, 567) has added support to this theory.

However, over the last two decades an overwhelming volume of data has been generated which make this theory seem implausible, and in some respects impossible. Firstly, only CGRP has been shown to be released during migraine, with no evidence of substance P or neurokinin A release (289, 325). Furthermore, of all the inflammatory molecules shown to induce dural and retinal plasma protein extravasation, only CGRP, a marker of a migraine attack, failed to produce a response (566). It has proven very difficult to induce plasma protein extravasation in human skin, a process that is readily induced in guinea pigs, implying there may be a clear

species difference that negates these preclinical studies (660). Also retinal plasma protein extravasation is not present during migraine (587) and there is little evidence of inflammatory pathology in migraineurs. Further, a plethora of molecules developed to block extravasation without the vasoconstrictive effects of triptans, including neurokinin 1 receptor antagonists (349, 351) and extravasation inhibitors (233, 691) failed as both acute and preventive treatments of migraine. These data indicate that it is unlikely that neurogenic dural inflammation plays a significant role in the pathophysiology of migraine, and the fact migraine can be so frequent and debilitating, and occur over many years, such an inflammatory insult would likely leave a pathology that is picked up on imaging, but nothing has been found (648).

Today migraine is more commonly described as a '*neurovascular disorder*', and specifically a disorder of the brain. One theory that has grown in significance over the last 15 years extolling this view, and has served to explain many features of migraine previously unexplored or simply not clear is '*peripheral and central sensitization'*. Sensitization is a common feature of many chronic pain disorders and is hypothesized to also be present during migraine. It is long-lasting activation and sensitization of peripheral nociceptors and central nociceptive neurons, and it may explain the longevity of the migraine attack, and the transition to chronic migraine, as well as specific related symptoms. This theory was borne out of experimental studies on rodents using an inflammatory soup placed upon the dura mater to induce peripheral and central sensitization of trigeminovascular neurons (766). Within the inflammatory soup are chemical mediators; histamine, serotonin and cytokines, that are believed to be released as a consequence of the dural inflammation and plasma protein extravasation, which complicates

the efficacy of this theory given the data regarding neurogenic dural inflammation. Certainly, peripheral sensitization of trigeminal nociceptive afferents that innervate the dural meninges has gone some way to explain the likely exacerbation of intracranial headache pain due to physical activity and movement, as well as the throbbing nature of pain during migraine (766). Central sensitization of trigeminovascular neurons has aided our understanding of the neural basis for extracranial hypersensitivity in migraine; the referral of pain and allodynia to peri-orbital and cutaneous facial areas (91, 135). Sensitisation of trigeminothalamic neurons is likely to account for the widespread cutaneous allodynia to extracephalic regions (128, 132).

A major tenet of this theory is that the primary trigger of migraine comes from the periphery, in the dural blood vessels, with activation of the trigeminovascular system coming from firing of first-order peripheral trigeminal neurons in response to nociceptive injury or signals coming from the meninges that release neuro-inflammatory mediators. Sustained activation of dural meningeal nociceptive neurons causes sequential activation and sensitization of first (peripheral nociceptors), second (at the level of the TCC) and third-order (trigeminothalamic) trigeminovascular neurons, as well as ascending activation of brainstem and other diencephalic structures (91). This sequential activation is thought to explain the throbbing nature of pain in migraine, the noxious sensory hypersensitivity, associated neurological symptoms including nausea, vomiting, altered feeding and sleep, as well as cognitive disruption. In principle the theory seems to address every symptom of migraine with the initial symptom or trigger being head pain, and everything else following as a consequence. Clinically however, there are many gaps. Premonitory symptoms in migraine can be present 24-48 hours prior to headache, and

are represented by changes in activation in midbrain and hypothalamic brain regions (300, 559). Migraine triggers such as sleep and food deprivation, and stress, are under homeostatic control, likely via the hypothalamus and midbrain structures, and they do not directly activate the meninges. They do however modulate nociceptive inputs to the TCC through descending mechanisms, and have ascending projections to the cortex, and with these as trigger it is likely headache would not be the first sign of the disease. As reported there is little evidence of vasodilation during migraine, which one would assume to be a consequence of release of inflammatory mediators and activation of nociceptive nerve fibers that innervate the meninges. Therefore while sensitization of trigeminovascular pathways is clearly important, the mechanism that drives this response is not clear.

Despite these clinical anomalies as outlined above, there remains a strong belief that CSD the experimental correlate for aura is the primary triggering event for meningeal activation (the evidence for and against has been discussed above). As mentioned, aura is only present in approximately in one third of migraineurs, although a common hallmark in the rare genetically identified forms. It is unlikely that all the different forms of migraine, (migraine with (MA) and without aura (MoA), FHM (645) and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (151, 451), are all a consequence of different pathophysiological mechanisms. Given that most MA patients also suffer MoA and FHM patients can present with MA and MoA, it would suggest that a common pathophysiology underlies the conditions with heterogeneity amongst the associated symptoms that is certainly influenced by genetic predisposition.

Stepping back from CSD, it is perhaps pertinent to explore the role of the cortex itself. There is contradictory evidence of cortical excitability in migraine, on one hand migraineurs are more susceptible to visual triggering and have heightened sensitivity to such stimuli. This may result from hyperexcitability, particularly in MA (169), with a decreased threshold to produce phosphenes (82, 122, 298). However, there are similar reports of hypoexcitability states and significantly higher phosphene thresholds (8, 182). An elegant review of the data concluded that these observed changes in cortical excitability may not actually be a predisposition factor to develop migraine, but rather that changes in neuronal excitability are a function of the chronicity process in the disease (750) and an example of when in the cycle patients were tested. It would appear more reasonable to assume that altered cortical switching between hypo and hyper-excitable states exists resulting in dysregulation of normal cortical function. Alternatively much of the evidence supporting the hyperexcitability may result from lower order trigeminovascular alterations via thalamocortical networks, such as the recently identified thalamic involvement in photophobia (reviewed earlier (632)).

In the case of MoA, if CSD is the triggering factor of attacks then patients must demonstrate cortical changes similar to CSD without the physical symptoms (silent aura). There also needs to be explanations for the examples of aura without pain, or indeed treatments that improve aura, but not pain (340), but these are limited. We know that CSD has been very difficult to demonstrate in humans *in situ* and the only unequivocal evidence has been in injured human cortex (259, 589, 768). Recent studies supporting CSD in human brain during migraine aura

(366, 702) only use blood flow evidence rather than neuronal changes, which is what technically defines CSD, and merely provide more sophisticated technology to measure the response than the original study from the 1980s (640). But there is evidence from imaging studies of unilateral occipital hypoperfusion prolonged well into the headache phase of migraine with aura (640, 702), while the aura symptoms do not persist. This could be interpreted as a demonstration of aura pathophysiology without aura symptoms and similar mechanisms could hypothetically be involved in migraine without aura. However, in MoA there is much conflicting information regarding hypoperfusion, with several studies demonstrating no perfusion changes during MoA, particularly during the headache phase (192, 702) while a more recent study demonstrated prolonged bilateral posterior cerebral hypoperfusion, and this continued beyond pain relief with sumatripan (210). It is worth noting that global hypoperfusion has also been demonstrated simply in response to pain (173). Therefore it is unlikely that CSD can explain prolonged bilateral hypoperfusion in this case. CSD is described as a wave that requires dense populations of neurons to spread across the cortex, therefore hemispheric boundaries cannot be negotiated. Recently it has been hypothesised there may be a dissociation between the neuronal and vascular responses to CSD, with evidence that vasomotor changes spread at greater velocities to the metabolic/neuronal changes (120, 153). As such, it could be hypothesized that independent mechanisms, which do not involved CSD, but result in similar vasomotor physiology, may underlie the prolonged hypoperfusion that has been demonstrated in migraine with and without aura.

The final disparity between MA and MoA lies in the epidemiology of the conditions as risk factors for other disorders. It was recently demonstrated that FHM mice undergoing experimental stroke suffered greater brain damage and poorer outcomes than control mice. It seems migraine mutations increase stroke vulnerability by facilitating ischemic depolarizations. Clinically, MA is a risk factor for stroke (483), especially in females although not for MoA (487, 716) which is indicative of at the very least significantly fewer CSD events in MoA. There is therefore uncertainty and continuing debate about the role of aura in the cascade of events resulting in migraine pain and accompanying symptoms, which will likely continue due to the complex nature of the disease rendering it difficult to separate the component parts in a feasible manner.

If the triggering of migraine does not come from the periphery or cortical spreading depression, how can the provocation of a migraine attack be explained?

While migraine pain is undoubtedly a consequence of activation, or the perception of activation of neurovascular mechanisms, as a disorder it is now being thought of by some as a purely neuronal disorder. Much evidence indicates that the brains of migraineurs may be different in how they respond to sensory stimulation, even interictally (116, 158, 182, 749). An alternative and all-encompassing hypothesis is that the brain is at the heart of triggering migraine. Rather than a sequential activation of different brain regions, migraine is a disorder of the brain and therefore considered a '*brain state*', and is a consequence of changes, or dysfunction, in brainstem and hypothalamic regions, which contribute to changes in cellular and vascular

function in many regions of the brain. This hypothesis states that migraine may be best described as a consequence of dysfunction in the brainstem and hypothalamic nuclei that normally modulate or gate sensory inputs, including touch, light, sounds, and smells. These brainstem and hypothalamic nuclei can be considered '*migraine mediators*' and their dysfunction can lead to the failure of brain integration and filtering mechanisms, resulting in the perception of activation of sensory systems under normal conditions. The complex network of connections between regions of the brainstem, which include the PAG, RVM, locus coeruleus and SuS, and diencephalic nuclei including hypothalamus, thalamus and cortex can lead to the generation of symptoms through the same core dysfunction. Dysfunction in these regions, through descending control of trigeminovascular nociceptive traffic, can lead to the perception of head pain through normal vessels throbbing, and continued dysfunction can lead to central sensitization of trigeminovascular neurons and the exacerbation of pain to normal physical activity, cutaneous cephalic and extracephalic allodynia. Convergence of sensory inputs in the thalamus that project to the cortex can explain the hypersensitivity to light, sounds, and smells. The same dysfunction can lead to homeostatic changes, controlled by the hypothalamus, related to sleep, feeding, and activity. The general alteration of cortical and subcortical function can trigger events such as migraine aura, and extend to a general inability to function properly. Inherited genetic factors clearly play a role in pre-disposing migraine susceptibility, as do the role of potential migraine triggers, whose common link seems to play at the heart of brain homeostasis in the hypothalamus and brainstem.

Certainly much is still unclear about how we understand migraine. It is most likely that many of the ideas surrounding its pathophysiology are relevant, from a genetic predisposition, to brain hyperexcitability, to peripheral and central sensitization, and brainstem and hypothalamic dysfunction. They all contribute to the phenotype of the migraineur and are avenues that need to be explored further to understand the pathophysiology of migraine, and the development of novel safer and effective migraine therapeutics.

Conclusion

Migraine is a complex, basically inherited variable disorder of brain function. Its afferent pathway arises in the nociceptive durovascular afferents that seemed design to warn not localize. Their projection to the thalamus and cortex, and the regulation of this pathway, importantly at each level, and by multiple systems offers the possibility to understand the complex symptoms and target therapies. Migraine is a trait, well demonstrated by neurophysiological data that waxes and wanes to attacks. The attacks start as premonitory symptoms, such as concentration impairment, yawning, mood change, homeostatic changes-eating and fluid balance, and can include more generalized sensitivities, such as photophobia and phonophobia. The premonitory phase gives way to the pain phase with its attendant suffering and terminates in a postdromal phase of feeling washed out by the experience. Migraine aura, at least in its classical sense has some relationship to cortical spreading depression, although this is neither necessary nor sufficient for the attack, more likely acting as a parallel actor on an arguably smaller stage. A crucial advance in understanding has been the

re-appreciation of migraine as a predominantly neural disorder with the development of non-vasoactive acute and preventive strategies for treatment. Understanding migraine both offers the tangible benefit of reducing the burden of the sixth most disabling medical problem on the planet and the real opportunity to gain insights in basic aspects of human neurobiology. Migraine pathophysiology has come a long way in the last two millennia and seems poised to accelerate the pace and deliver even more benefits the in the coming decades.

Table 1: International classification for headache disorders (ICHD)-3β (386)

Criteria for migraine without aura

A. At least five attacks fulfilling criteria B-D

B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

C. Headache has at least two of the following four characteristics:

    1. unilateral location

    2. pulsating quality

    3. moderate or severe pain intensity

    4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D. During headache at least one of the following:

    1. nausea and/or vomiting

    2. photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis

Criteria for migraine with aura

A. At least two attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:

    1. visual

    2. sensory

    3. speech and/or language

    4. motor

    5. brainstem

    6. retinal

C. At least two of the following four characteristics:

    1. at least one aura symptom spreads gradually over ≥ 5 minutes, and/or two or more symptoms occur in succession

    2. each individual aura symptom lasts 5-60 minutes

    3. at least one aura symptom is unilateral

4. the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

Table 2: Summary of craniovascular nerve fibers and their vasoactive neuropeptides involved in migraine

Craniovascular nerve fiber localization	Vasoactive neuropeptide/Neurotransmitter
Trigeminal Sensory Nerve Fibers	• Calcitonin gene-related peptide (CGRP) • Substance P (SP) • Neurokinin A (NKA) • Pituitary adenylate cyclase-activating peptide (PACAP) • Nitric oxide synthase (NOS)
Parasympathetic Nerve Fibers	• Vasoactive intestinal peptide (VIP) • PACAP • Neuropeptide Y (NPY), • Acetylcholine • NOS
Sympathetic Nerve Fibers	• Noradrenaline, • NPY • Adenosine triphosphate (ATP)

Table 3: Summary of neuropeptides and their role in homeostatic function

Neuropeptide	Effect on appetite	Receptors	Food restriction	Refeeding	Sleep deprivation	Normal sleep	Physiological stress	Migraineurs
Leptin	Anorexigenic (reduces appetite)	ObR(a-f) leptin signaling through ObRb	↓ leptin plasma levels ↑ leptin binding in ARC	↑ leptin secretion	↓ leptin plasma levels	↑ leptin plasma levels	Leptin ↓ glucocorticoid secretion	Lower serum leptin interictally
Neuropeptide Y (NPY)	Orexigenic (increases appetite)	NPY Y(1-6) Only Y1, Y2, Y4 and Y5 physiologically relevant	↑ NPY mRNA in ARC ↑ secretion of NPY into PVN	Normalizes NPY levels in ARC ↑ NPY in PVN	↑ NPY hypothalamic mRNA levels	NPY promotes sleep	↑ NPY in the PVN ↑ACTH and corticosterone release	ND
Orexin (OX) A and B	Orexigenic	OX_1R and OX_2R	↑ Ox release hypothalamus ↑ OX_1R VMH mRNA ↑ OX_2R ARC mRNA	↑ prepro-orexin mRNA in LH	↑ mRNA Ox levels in hypothalamic	Ox neurons stop firing during sleep	Orexin ↑ glucocorticoid secretion	Higher CSF OxA levels in CM/MOH

↑, increase; ↓ decrease; ARC, hypothalamic arcuate nucleus; PVN, paraventricular hypothalamic nucleus; VMH, ventromedial hypothalamic nucleus; CM, chronic migraine; MOH, medication overuse headache; ND, no data

Table 4: Current developmental pipeline in migraine (modified after306)

Mechanism/Indication	Treatment	Current Stage
Calcitonin gene-related peptide (CGRP) mechanism antagonist		
• CGRP receptor antagonist (*gepant*)	Olcegepant (638)	Phase II
	Telcagepant- acute (396)	Phase II*
	Telcagepant- preventive (394)	Phase II
	Rimagepant (561)	Phase II
	BI44370TA (216)	Phase II*
	MK-3207 (391)	Phase II
	Ubrogepant (828)	Phase II
	AGN-241689 (preventive)¶	Phase I
• CGRP antibody (-*nezumab*)	ALD-403 (224)	Phase III
	galcanezumab (225)	Phase III
	TEV-48125 (96, 97)	Phase III
• CGRP receptor antibody (-*numab*)	erenumab (770)	Phase III
Serotonin-related		
Serotonin 5-HT_{1F} receptor agonist- (*ditan*)	Lasmiditan (260, 267)	Phase III
Nitric oxide synthase (NOS) inhibition		
• Pan NOS	546C88 (507)	Phase II
• Inducible NOS		
	GW274150 acute (649)	Phase II (F)
	GW274150 preventive (403)	Phase II (F)
• Neuronal NOS plus triptan	NXN-188 (428, 595)	Phase II (F)
Glutamatergic targets		

• NMDA receptor migraine with prolonged aura	Ketamine (10)	Phase II
• Prevention of aura not headache	Tonabersat (326, 381)	Phase II
• AMPA/kainate	Tezampanel/LY293558 (704)	Phase II
• iGluR5 (kainate) receptor	LY466195 (448)	Phase II
• mGluR5 (glurants)	ADX10059 (839)	Phase II
• AMPA receptor antagonist	BGG492 (353)	Phase II (F)
Neuroinflammatory targets		
• TRPV1	SB-705498(165)	Phase II (F) Phase II (F)
• Substance P/neurokinin-1	Dapitant (218) Lanepitant (351) GR205171 (176) L-758,298 (629) Lanepitant (349) Prevention	Phase II (F) Phase II (F) Phase II (F) Phase II (F) Phase II (F)
• Neurogenic plasma protein extravasation (PPE)	CP-122,288 (691) 4991W93 (233)	Phase II (F) Phase II (F)
Other targets		
• Orexin 1 and 2 receptors (*rexants*)	Fliorexant (150)	Phase II (F)
• Angiotensin Receptor (?)	Candesartan (765, 800) Telmisartan (219)	Off-License (F)
Emerging targets		
• Acid Sensing Ion Channel (ASICs)	Amiloride (406)	
• Pituitary adenylate cyclase activating peptide (PACAP)	PACAP receptor antagonists (17, 41, 874)	

• Neuronal NOS	Neuronal NOS inhibition (310)	
• Phosphodiesterase inhibition	Ibudilast (514)	
Neuromodulation strategies		
Transcranial magnetic stimulation (TMS)	Single Pulse TMS (94, 537)	Marketed
Occipital nerve stimulation (ONS)	Chronic migraine (538, 705, 735)	Phase II (F)
Transcutaneous vagal nerve stimulation	Gammacore device (327, 736)	Phase II (F)
Supraorbital nerve stimulation	Cefaly (711)	Marketed
Sphenopalatine ganglion stimulation	ATI device (NCT01540799)	Phase II

(F)- Study failed; *Liver toxicity led to termination of development; ¶Reported to exist in November 2015 at Allergan R&D Day

Figure 1 The migrainous brain interictally

Imaging studies in the migraineurs' brain interictally demonstrates there is reduced activation of the spinal trigeminal nuclei in response to trigeminal nociceptive stimulation, which normalizes prior to the next migraine attack. This change might reflect an increased susceptibility of the brain to generate the subsequent attack in the sense of a defective top-down modulation of trigeminal input (taken with permission from 749).

Figure 2 The migrainous migraine during the premonitory phase

In nitroglycerin-induced migraine attacks $H_2{}^{15}O$-PET demonstrated increased rCBF in the posterior hypothalamic region (A and B), the periaqueductal grey region (C and D), and in dorsal pons (E and F) are highlighted by circles. The color bar indicates the color coding of the Z scores. (559). From a clinical perspective, the hypothalamus might be involved in the premonitory symptoms prior to the experience of head pain. Such symptoms involve tiredness, concentration problems, yawning, appetite alterations, and frequent urination. Activation in the midbrain and PAG likely reflects a mechanism through which nociceptive head pain symptoms may be generated (Taken with permission from 559).

Figure 3 The migrainous brain during migraine head pain

Many studies have demonstrated that migraine attacks are associated with an increase of rCBF in mesencephalon and pons, which cannot be found in experimental head pain, indicating specificity for migraine attacks (842). After termination of the migraine attack with sumatriptan these changes persisted, suggesting involvement in migraine generation or sustentation, rather than specifically trigeminally-mediated pain.

Figure 4 Anatomy of the trigeminovascular system – ascending projections

The trigeminal ganglion (TG) gives rise to pseudo-unipolar trigeminal primary afferents which synapse on intra and extra-cranial structures (blood vessels) as well as the spinal cord trigeminocervical complex (TCC). Second order neurons from the TCC ascend in the quintothalamic (trigeminothalamic) tract synapsing on third order thalamocortical neurons. Direct and indirect ascending projections also exist to the locus coeruleus (LC), periaqueductal grey (PAG) and hypothalamus. The third order thalamocortical neurons in turn synapse on a diffuse network of cortical regions including the primary and secondary motor (M1/M2), somatosensory (S1/S2) and visual (V1/V2) cortices. A reflex connection from the TCC to the superior salivatory nucleus (SuS) exists, which projects via the sphenopalantine ganglion (SPG) providing parasympathetic innervation to the extra and intra-cranial structures. Insula; Ins, Parietal Association; PtA, Retrosplenial; RS, Auditory; Au, Ectorhinal; Ect, Rostral ventromedial medulla; RVM.

Figure 5 Modulation of trigeminovascular nociceptive transmission – descending projections

The trigeminocervical complex (TCC) is subject to direct and indirect descending pain modulatory pathways arising in the cortex. Direct projections exist from primary somatosensory (S1) and Insular (Ins) cortices while indirect projections arising in S1 that project via the hypothalamus. A local corticothalamic circuit also exists which can modulate trigeminothalamic processing. Hypothalamic projections again form direct TCC modulatory projections as well as indirect projections via the locus coeruleus (LC) and periaqueductal gray (PAG) which can further pass via the rostral ventromedial medulla (RVM). This complex network of direct and indirect pathways provides potent anti- and pro-nociceptive modulation of incoming trigeminal nociceptive signaling, the dysfunction of which is thought to contribute to triggering migraine attacks. Sphenopalantine ganglion; SPG, superior salivatory nucleus; SuS, trigeminal ganglion; TG.

Figure 6 Anatomy of the trigemino-autonomic pathway believed to contribute to head pain and cranial autonomic symptoms in migraine.

A) Schematic representation of trigemino-autonomic pathway includes the peripheral and central projections of the trigeminovascular system (black neurons). There is also a trigemino-autonomic reflex connection from the trigeminocervical complex (TCC; grey neuron), to the superior salivatory nucleus (green cell; SuS) and its parasympathetic projection to the cranial vasculature, predominantly via the greater petrosal nerve (green projection) and its synapse with the pterygopalatine ganglion (PG), as well as via the facial (VIIth cranial) nerve (purple neuron). **B)** Electrophysiological recording of neurons in the rat TCC is activated by SuS stimulation, firstly there is a shorter latency response **(C)** believed to be activated by antidromic activation of the trigemino-autonomic reflex, and a longer latency response **(C and D)** caused by activation of the parasympathetic outflow to the cranial vasculature; a signal which traverses the nociceptive meninges, which subsequently causes activation of the central trigeminovascular projection to the TCC. **E)** Lacrimal gland/duct (yellow cell in **B**) blood flow also increases concurrent with SuS stimulation, as a result of the parasympathetic projection to the lacrimal gland. TG; trigeminal ganglion. (Parts C-E are modified from 25, 26).

Figure 7 Proposed mechanism of descending modulation of trigeminovascular nociceptive transmission through brainstem nuclei, mediated by 5-HT and endocannabinoids

A) The spontaneous firing of neurons in the TCC is modulated by micro-injection of CB_1-mediated endocannabinoids (ACPA) in the ventrolateral periaqueductal grey (vlPAG), with transient inhibition of firing. **B)** ACPA micro-injection in the vlPAG also inhibits dural-evoked nociceptive firing in the TCC, an effect that is replicated by naratriptan micro-injection. We propose that the mechanism of action of this inhibitory effect is by modulating descending GABAergic projections **C and D)**. At the level of the vlPAG GABAergic projection (blue) neurons synapse with glutamatergic projections (purple) to 'OFF' and 'ON' cells in the rostral ventromedial medulla (RVM). Tonic release of GABA (blue circles) controls the level of descending inhibition to the TCC, via 'OFF' and 'ON' cell activity in the RVM. Cannabinoid (CB_1, green) and triptan ($5\text{-}HT_{1B/1D}$, orange) receptors are located pre-synaptically on these GABAergic projections. Orexin 1 (Ox1, red) receptors are also located post-synaptically on the glutamatergic projections. Endogenous release or exogenous administration of ECs (green circles) and 5-HT agonists (yellow circles) activate pre-synaptic receptors inhibiting the release of GABA, increasing the likelihood of activation of the descending glutamatergic projections to 'OFF' cells in the rostral ventromedial medulla (RVM). Activation of post-synaptic Ox1 receptors are also thought to stimulate the production and release of ECs from the post-synaptic cell, activating pre-synaptic CB_1 receptors and inhibiting GABA release, disinhibiting, and thus activating glutamatergic projections to 'OFF' cells in the RVM. This implies that orexin peptides may also be involved in this mechanism of descending control. **D)** At the same time a hypothesized projection (dashed lines) from the descending glutamatergic projection also

synapses with an inhibitory interneuron (light blue neuron-dashed lines) in RVM, which inhibits activity of 'ON' cells. Activation of RVM 'OFF' cells and inhibition of 'ON' cell results in switching off activity at the level of the trigeminocervical complex (TCC) second order neuron.

D) Additionally at the level of the RVM CB_1 receptors situated pre-synaptically on GABAergic projections to 'OFF' cells, when activated by endogenous or exogenous ECs, inhibit the release of GABA, increasing 'OFF' cell activity by disinhibition, likewise we propose that pre-synaptic CB_1 receptors on glutamatergic projections to 'ON' cells inhibit the release of glutamate blocking 'ON' cell activation, and thus reducing activity at the level of the TCC. 'ON' cell activity may also be inhibited by CB_1 receptor-mediated inhibition of pre-synaptic release of GABA from neurons that synapse on inhibitory interneurons (light blue neuron-dashed lines). There is also thought to be a state-dependent and bidirectional control of pain modulation through serotonergic projections from the RVM to the TCC that is distinct to 'ON' and 'OFF' cell modulation. (Data in A and B adapted from24).

Figure 8 Proposed mechanisms for the neural basis of photophobia in migraine

A) It is proposed that there is convergence of photic signals from the retina, via an intact optic nerve, onto posterior thalamic neurons that also receive nociceptive inputs from the dura mater, via the trigeminothalamic tract. These inputs subsequently project to nociceptive areas of the cortex (S1 and S2) resulting in the exacerbation of migraine headache by light, and areas of the visual cortex that cause hypersensitivity to light itself. **B)** PET imaging during the interictal phase of migraine demonstrates that 600-1800 Cd/m^2 light causes activation in the visual cortex in migraineurs, whereas in controls there is no activation (lower panel). During pain in the trigeminal distribution light does causes activation in the visual cortex of control subjects, and a hypersensitive response in the visual cortex of migraineurs. **C).** During migraine low intensity light (240 Cd/m^2) also causes activation in the visual cortex which is significantly greater compared to that after headache relief with sumatriptan and headache-free interval. Also activation of the visual cortex to the low level light after headache relief is still greater than that during headache-free interval. These data indicate that further physiological mechanism may contribute to the hypersensitivity to light as it appears to be not dependent on a trigeminovascular nociceptive input. (Parts B and C are taken and adapted from 116, 208).

Figure 9 Anatomy and pharmacology of the hypothalamic nuclei and brainstem nuclei involved in energy homeostasis and pain modulation in the context of migraine

Projections to and from specific nuclei within the hypothalamus are involved in the complex neural circuitry of energy homeostasis, including the arcuate (ARC), paraventricular (PVN), ventromedial (VMH), dorsomedial (DMH) and lateral (LH) hypothalamic neurons. In the ARC energy homeostasis is controlled by orexigenic neuropeptides (stimulating (+) food intake and decrease energy expenditure) neuropeptide Y (NPY) and agouti-related peptide (AgRP) and anorexigenic peptides (inhibit (-) food intake and increase energy expenditure) proopiomelanocortin (POMC) and cocaine-and amphetamine-regulated transcript (CART). Peripheral circulating hormones insulin and leptin inhibit NPY/AgRP and stimulate POMC/CART neurons. Communication amongst these neural circuits is further controlled by the release of orexin A and B, corticotropin-releasing factor (CRF), melanin-concentrating hormone (MCH), γ-aminobutyric acid (GABA), glutamate (GLU) and brain-derived neurotrophic factor (BDNF), amongst others. The role these nuclei have in potentially triggering migraine, as a consequence of altered feeding and changes in energy homeostasis, is through their descending projections to brainstem nuclei known to be involved in the modulation of pain processing related to headache. These include direct PVN projections to the trigeminocervical complex (TCC), VMH projections the periaqueductal grey (PAG) and the locus coeruleus (LC), and indirect communication through the ventral tegmental area (VTA) and nucleus tractus solitarius (NTS). Hypothetically altered feeding will affect neuronal processing in the ARC, and subsequently in other hypothalamic nuclei through its connections to them, including the PVN, VMH and LH. Their control of transmission of nociceptive inputs to the trigeminovascular system may be

altered, which ultimately produces the perception of noxious input from the craniofacial region and activation of trigeminovascular system, with a specific injury or insult.

NPY receptors, NPY1R and NPY5R; orexin receptors, OX1R and OX2R, long ‘signaling’ isoform of the leptin receptor, ObRb; insulin receptor, INSR and 3rd ventricle, 3V

Acknowledgements

The authors thank Michele Lasalandra for excellent technical assistance with many of the studies over a long period.

Work reported herein has been supported by the Sandler Foundation, The European Union (EUROHEADPAIN- EU 602633), The Wellcome Trust and the Department of Defense. Margarida Martins Oliveira was funded by the Portuguese Fundação para a Ciência e Tecnologia (FCT) with an individual PhD grant (SFRH/BD/ 77127/2011).

Some parts of the King's CRF are funded by the South London and the Maudsley Mental Health BRC. The views expressed are those of the author(s) and not necessarily those of the UK NHS, the NIHR or the Department of Health.

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