Primary headache is a common problem in neurology. The main disabling form of primary headache presenting to neurologists is migraine, either episodic or chronic. Migraine is an inherited disorder of the brain that involves dysfunction of subcortical structures that modulate sensory input. Its therapy involves reducing afferent traffic or stabilizing these abnormal pathways. Understanding the pathophysiology of migraine is integral to providing explanations to patients and good management strategies.

Headache in general, and in particular migraine (Goadsby et al, 2002), is better understood now than has been the case for the last four millennia (Lance and Goadsby, 2005). Migraine is a common (Lipton et al, 2001), disabling (Menken et al, 2000), recurrent disorder of the central nervous system in which core manifestations involve activation, or the perception of activation, of trigeminal nociceptive afferents. This chapter will explore the anatomy and physiology that underpins the commonest of the neurological problems. An understanding of the pathophysiology of migraine will enable the clinician to explain many things to patients, including the limits of what is known and the basis upon which therapeutic approaches are currently employed.

The essential elements to be considered are:
- Genetics of migraine
- Physiological basis for the aura
- Anatomy of head pain, particularly that of the trigeminovascular system
- Physiology and pharmacology of activation of the peripheral branches of ophthalmic branch of the trigeminal nerve
- Physiology and pharmacology of the trigeminal nucleus, in particular its caudal most part, the trigeminocervical complex
- Brain stem and diencephalic modulatory systems that influence trigeminal pain transmission and other sensory modality processing, including data from functional brain imaging

MIGRAINE—EXPLAINING THE CLINICAL FEATURES

Migraine is in essence a familial episodic disorder whose key marker is headache with certain associated features (Table 3-1). It is these features that give clues to its pathophysiology and ultimately will provide insights leading to new treatments.

GENETICS OF MIGRAINE

One of the most important aspects of the pathophysiology of migraine is the inherited nature of the disorder. It is clear from clinical practice that many patients have first-degree relatives who also suffer from migraine (Lance and
Transmission of migraine from parents to children has been reported as early as the 17th century, and numerous published studies have reported a positive family history. Genes and Environment Studies of twin pairs are the classic method to investigate the relative importance of genetic and environmental factors. A Danish study included 1013 monozygotic and 1667 dizygotic twin pairs of the same gender, obtained from a population-based twin register (Ulrich et al, 1999). The pair-wise concordance rate was significantly higher among monozygotic than dizygotic twin pairs (P < .05). Several studies have attempted to analyze the possible mode of inheritance in migraine families, and conflicting results have been obtained. Both twin studies and population-based epidemiological surveys strongly suggest that migraine without aura is a multifactorial disorder, caused by a combination of genetic and environmental factors.

**Familial Hemiplegic Migraine**

In approximately 50% of the reported families, familial hemiplegic migraine (FHM) has been assigned to chromosome 19p13. Few clinical differences have been found between chromosome 19-linked and chromosome 19-unlinked FHM families. Indeed, the clinical phenotype does not associate particularly with the known mutations (Ducros et al, 2001). The most striking exception is cerebellar ataxia, which occurs in approximately 50% of the chromosome 19-linked but in none of the chromosome 19-unlinked families. Another less striking difference includes the fact that patients from chromosome 19-linked families are more likely to have attacks that can be triggered by minor head trauma or that are associated with coma.

The biological basis for the linkage to chromosome 19 is mutation (Ophoff et al, 1996) involving the Ca_v2.1 (P/Q) type voltage-gated calcium channel (Ertel et al, 2000) CACNA1A gene. Now known as FHM-I, this mutation is responsible for about 50% of identified families. Mutations in the ATP1A2 gene (De Fusco et al, 2003) have been identified to be responsible for about 20% of FHM families. Interestingly, the phenotype of some FHM-II involves epilepsy, while it has also been suggested that alternating hemiplegia of childhood can be due to ATP1A2 mutations. The latter cases are most unconvincing for migraine. Most recently, mutations in the voltage-gated sodium channel gene SCN1A have been identified as the cause for FHM-III (Dichgans et al, 2005). The phenotype of mutations in this gene

**TABLE 3-1**

**International Headache Society Features of Migraine**

Repeated Episodes of Headache (4 to 72 Hours) With the Following Features:

- Any Two of:
  - Unilateral
  - Throbbing
  - Worsened by movement
  - Moderate or severe

- Any One of:
  - Nausea/vomiting
  - Photophobia and phonophobia

Headache Classification Subcommittee of The International Headache Society. The International Classification of Headache Disorders. 2nd edition. Cephalalgia 2004;24(suppl 1):9–160.

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Goadsby, 2005; Silberstein et al, 2002). Transmission of migraine from parents to children has been reported as early as the 17th century, and numerous published studies have reported a positive family history.

**Genetic Epidemiology**

Studies of twin pairs are the classic method to investigate the relative importance of genetic and environmental factors. A Danish study included 1013 monozygotic and 1667 dizygotic twin pairs of the same gender, obtained from a population-based twin register (Ulrich et al, 1999). The pair-wise concordance rate was significantly higher among monozygotic than dizygotic twin pairs (P < .05). Several studies have attempted to analyze the possible mode of inheritance in migraine families, and conflicting results have been obtained. Both twin studies and population-based epidemiological surveys strongly suggest that migraine without aura is a multifactorial disorder, caused by a combination of genetic and environmental factors.
KEY POINT:
- Taken together, the known mutations in familial hemiplegic migraine suggest that migraine, or at least the neurological manifestations currently called the aura, are caused by an ionopathy.

can also feature epilepsy, although interestingly the identified families had FHM alone.

Taken together, the known mutations suggest that migraine, or at least the neurological manifestations currently called the aura, are caused by an ionopathy (Goadsby and Kullmann, 2005). Linking the channel disturbance for the first time to the aura process has demonstrated that human mutations expressed in a knock-in mouse produce a reduced threshold for cortically spreading depression (van den Maagdenberg et al, 2004).

MIGRAINE AURA
Migraine aura is defined as a focal neurological disturbance manifesting as visual, sensory, or motor symptoms (Headache Classification Subcommittee of the International Headache Society, 2004). It is seen in about 30% of patients, and it is clearly neurally driven (Cutrer et al, 1998). The case for the aura being the human equivalent of the cortically spreading depression of Leao has been well made (Lauritzen, 1994). In humans, visual aura has been described as affecting the visual field, suggesting the visual cortex, and it starts at the center of the visual field and propagates to the periphery at a speed of 3 mm/min across the cortex. Human aura has been well described using functional imaging methods to behave in a similar fashion (Hadjikhani et al, 2001). An area of controversy surrounds whether aura in fact triggers the rest of the attack and is indeed painful (Moskowitz et al, 2004). Based on the available experimental and clinical data, this author is not at all convinced that aura is painful (Goadsby, 2001), but this does not diminish its interest or the importance of understanding it. Indeed therapeutic developments may shed even further light on these relationships.

HEADACHE—ANATOMY
Trigeminal Innervation of Pain-producing Intracranial Structures
Surrounding the large cerebral vessels, pial vessels, large venous sinuses, and dura mater is a plexus of largely unmyelinated fibers that arise from the ophthalmic division of the trigeminal ganglion and in the posterior fossa from the upper cervical dorsal roots. Trigeminal fibers innervating cerebral vessels arise from neurons in the trigeminal ganglion that contain substance P and calcitonin gene-related peptide (CGRP) (Uddman et al, 1985), both of which can be released when the trigeminal ganglion is stimulated either in humans or cats (Goadsby et al, 1988). Stimulation of the cranial vessels such as the superior sagittal sinus is painful in humans (Wolff, 1948). Human dural nerves that innervate the cranial vessels largely consist of small diameter myelinated and unmyelinated fibers that almost certainly subserve a nociceptive function (Table 3-2).

HEADACHE PHYSIOLOGY
Peripheral Connections
Plasma protein extravasation. Moskowitz (1990) has provided a series of experiments to suggest that the pain of migraine may be a form of sterile neurogenic inflammation. Although this seems clinically implausible as an explanation for the entire syndrome, the model system has been helpful in understanding some aspects of trigeminovascular physiology. Neurogenic plasma extravasation can be seen during electrical stimulation of the trigeminal ganglion in the rat. Plasma extravasation can be blocked by ergot alkaloids, indomethacin, acetylsalicylic acid, and the serotonin-5 hydroxytryptamine (HT)1B/1D agonist, sumatriptan (Moskowitz and Cutrer, 1993). In addition
to an inflammatory process, structural changes in the dura mater are observed after trigeminal ganglion stimulation. These include mast cell degranulation and changes in postcapillary venules, including platelet aggregation. While it is generally accepted that such changes, and particularly the initiation of a sterile inflammatory response, would cause pain (Burstein et al, 1998), it is not clear whether this is sufficient of itself or requires other stimulators or promoters. Preclinical studies suggest that cortically spreading depression may be a sufficient stimulus to activate trigeminal neurons (Bolay et al, 2002), although this has been a controversial area (Goadsby, 2001).

Although plasma extravasation in the retina, which is blocked by sumatriptan, can be seen after trigeminal ganglion stimulation in experimental animals, no changes are seen with retinal angiography during acute attacks of migraine or cluster headache (May et al, 1998b). A limitation of this study was the probable sampling of both retina and choroid elements in rat, given that choroidal vessels have fenestrated capillaries. Clearly, however, blockade of neurogenic plasma protein extravasation is not completely predictive of antimigraine efficacy in humans as evidenced by the failure in clinical trials of substance P–neurokinin-1 antagonists, specific plasma protein extravasation blockers, CP122,288 and 4991w93, an endothelin antagonist and a neurosteroid (Goadsby, 2005).

**Sensitization and migraine.** While it is highly doubtful that a significant sterile inflammatory response occurs

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**TABLE 3-2** Neuroanatomical Processing of Vascular Head Pain

| Component of Pain Pathway | Structure | Comments |
|---------------------------|-----------|----------|
| Target Innervation        |           |          |
| Cranial vessels           | Ophthalmic branch of trigeminal nerve |          |
| Dura mater                |           |          |
| First order neuron        | Trigeminal ganglion | Middle cranial fossa |
| Second order neuron       | Trigeminal nucleus (Quintothalamic tract) | Trigeminal nucleus caudalis and C1-2 dorsal horns |
| Third order neuron        | Thalamus | Ventrobasal complex |
|                           |           | Medial nucleus of posterior group |
|                           |           | Intralaminar complex |
| Modulatory                | Midbrain | Periaqueductal gray matter |
|                           | Hypothalamus | ? |
| Final                     | Cortex | Insulae |
| |

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**KEY POINTS:**

- The case for the migraine aura being the human equivalent of the cortical spreading depression of Leao has been well made.
- Human dural nerves that innervate the cranial vessels largely consist of small-diameter myelinated and unmyelinated fibers that almost certainly subserve a nociceptive function.
- Preclinical studies suggest that cortically spreading depression may be a sufficient stimulus to activate trigeminal neurons, although this has been a controversial area.
in the dura mater during migraine, it is clear that some form of sensitization takes place during migraine, since allodynia is common. About two thirds of patients report pain from nonnoxious stimuli, allodynia (Burstein et al, 2000; Selby and Lance, 1960). A particularly interesting aspect is the demonstration of allodynia in the upper limbs ipsilateral and contralateral to the pain. This finding is consistent with at least third-order neuronal sensitization such as sensitization of thalamic neurons and firmly places the pathophysiology within the central nervous system. Sensitization in migraine may be peripheral with local release of inflammatory markers, which would certainly activate trigeminal nociceptors. More likely, in migraine a form of central sensitization is present, which may be classical central sensitization (Burstein et al, 1998) or a form of disinhibitory sensitization with dysfunction of descending modulatory pathways (Knight et al, 2002). Just as dihydroergotamine can block trigeminovascular nociceptive transmission, probably at least by a local effect in the trigeminocervical complex, dihydroergotamine can block central sensitization associated with dural stimulation by an inflammatory soup.

Electrical stimulation of the trigeminal ganglion in both humans and the cat leads to increases in extracerebral blood flow and local release of both calcitonin gene-related peptide and substance P.

Neuropeptide studies. Electrical stimulation of the trigeminal ganglion in both humans and the cat leads to increases in extracerebral blood flow and local release of both calcitonin gene-related peptide and substance P (Goadsby et al, 1988). In the cat, trigeminal ganglion stimulation also increases cerebral blood flow by a pathway traversing the greater superficial petrosal branch of the facial nerve, again releasing a powerful vasodilator peptide, vasoactive intestinal polypeptide. Interestingly, the vasoactive intestinal polypeptide innervation of the cerebral vessels is predominantly anterior rather than posterior, and this may contribute to this region’s vulnerability to spreading depression, explaining why the aura is so very often seen to commence posteriorly. Stimulation of the more specifically vascular pain-producing superior sagittal sinus increases cerebral blood flow and jugular vein CGRP levels. Human evidence suggests that CGRP is elevated in the headache phase of migraine (Gallai et al, 1995; Goadsby et al, 1990). Moreover, nitric oxide (NO)–donor triggered migraine, which is in essence typical migraine (Iversen et al, 1989), also results in increases in CGRP (Juhasz et al, 2003) that are blocked by sumatriptan (Juhasz et al, 2005), just as in spontaneous migraine (Goadsby and Edvinsson, 1993). The recent development of nonpeptide highly specific CGRP antagonists, and the announcement of proof of concept for a CGRP antagonist in acute migraine (Olesen et al, 2004), firmly establish this as a novel and important new emerging principle for acute migraine. At the same time, the lack of any effect of CGRP blockers on plasma protein extravasation explains in some part why that model has proved inadequate at translation into human therapeutic approaches.

Central Connections
The trigeminocervical complex. Fos immunohistochemistry is a method for looking at activated cells by plotting the expression of Fos protein. After meningeal irritation with blood, Fos expression is noted in the trigeminal nucleus caudalis, while after stimulation of the superior sagittal sinus, Fos-like immunoreactivity is seen in the trigeminal nucleus caudalis and in the dorsal horn at the C1 and C2 levels in the cat and monkey. These latter findings are in accord with similar data using 2-deoxyglucose measurements with superior sagittal sinus stimulation. Similarly, stimulation of a branch of C2, the greater occipital nerve, increases metabolic activity in the same
regions, i.e., trigeminal nucleus caudalis and C1-2 dorsal horn. In experimental animals one can record directly from trigeminal neurons with both supratentorial trigeminal input and input from the greater occipital nerve, a branch of the C2 dorsal root (Bartsch and Goadsby, 2002). Stimulation of the greater occipital nerve for 5 minutes results in substantial increases in responses to supratentorial dural stimulation, which can last for more than an hour (Bartsch and Goadsby, 2002). Conversely, stimulation of the middle meningeal artery dura mater with the C-fiber irritant mustard oil sensitizes responses to occipital muscle stimulation (Bartsch and Goadsby, 2003). Taken together, these data suggest convergence of cervical and ophthalmic inputs at the level of the second-order neuron. Moreover, stimulation of a lateralized structure, the middle meningeal artery, produces Fos expression bilaterally in both cat and monkey brain. This group of neurons from the trigeminal nucleus caudalis and C1-2 dorsal horns should be regarded functionally as the trigeminocervical complex.

These data demonstrate that trigeminovascular nociceptive information comes by way of the most caudal cells. This concept provides an anatomical explanation for the referral of pain to the back of the head in migraine. Moreover, experimental pharmacological evidence suggests that some abortive antimigraine drugs, such as ergot derivatives, acetylsalicylic acid, sumatriptan, eletriptan, naratriptan, rizatriptan, and zolmitriptan, can have actions at these second-order neurons that reduce cell activity and suggest a further possible site for therapeutic intervention in migraine. This action can be dissected out to involve each of the 5-HT<sub>1B</sub>, 5-HT<sub>1D</sub>, and 5-HT<sub>1F</sub> receptor subtypes (Goadsby and Classey, 2003) and are consistent with the localization of these receptors on peptidergic nociceptors. Interestingly, triptans also influence the CGRP promoter and regulate CGRP secretion from neurons in culture (Durham and Russo, 1999). Furthermore, the demonstration that some part of this action is post-synaptic with either 5-HT<sub>1B</sub> or 5-HT<sub>1D</sub> receptors located non-presynaptically (Goadsby et al, 2001) offers a prospect of highly anatomically localized treatment options.

**Higher-order processing.** Following transmission in the caudal brain stem and high cervical spinal cord, information is relayed rostrally.

**Thalamus.** Processing of vascular nociceptive signals in the thalamus occurs in the ventroposteromedial (VPM) thalamus, medial nucleus of the posterior complex, and intralaminar thalamus. Zagami and Lambert (1991) have shown by application of capsaicin to the superior sagittal sinus that trigeminal projections with a high degree of nociceptive input are processed in neurons particularly in the VPM thalamus and its ventral periphery. These neurons in the VPM can be modulated by application of γ-aminobutyric acid (GABA)<sub>A</sub> inhibitory receptors, and perhaps of more direct clinical relevance by propranolol though β<sub>1</sub>-adrenoceptor mechanism (Shields and Goadsby, 2005). Remarkably, triptans through 5-HT<sub>1B</sub>/1D mechanisms can also inhibit VPM neurons locally, as demonstrated by microiontophoretic application, suggesting a hitherto unconsidered locus of action for triptans in acute migraine. Human imaging studies have confirmed activation of thalamus contralateral to pain in acute migraine (Afridi et al, 2005a; Bahra et al, 2001), cluster headache (May et al, 1998a), and in short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) (May et al, 1999).

**Activation of modulatory regions.** Stimulation of nociceptive afferents by stimulation of the superior sagittal sinus in the cat activates neurons in the
ventrolateral periaqueductal gray matter (PAG). PAG activation in turn feeds back to the trigeminocervical complex with an inhibitory influence (Knight et al, 2003). PAG is clearly included in the area of activation seen in positron emission tomography (PET) studies in migraineurs (Weiller et al, 1995). This typical negative feedback system will be further considered below as a possible mechanism for the symptomatic manifestations of migraine.

Another potentially modulatory region activated by stimulation of nociceptive trigeminovascular input is the posterior hypothalamic gray (Benjamin et al, 2004). This area is crucially involved in several primary headaches, notably cluster headache (Goadsby, 2002), SUNCT (May et al, 1999), paroxysmal hemicrania (Matharu et al, 2005), and hemicrania continua (Matharu et al, 2004b). Moreover, the clinical features of the premonitory phase (Giffin et al, 2003) and other features of the disorder suggest dopamine neuron involvement. Orexinergic neurons in the posterior hypothalamus can be both pronociceptive and antinociceptive (Bartsch et al, 2004), offering a further possible region whose dysfunction might involve the perception of head pain.

Central Modulation of Trigeminal Pain

Brain imaging in humans. Functional brain imaging with PET has demonstrated activation of the dorsal midbrain, including the PAG, and in the dorsal pons, near the locus coeruleus, in studies during migraine without aura (Weiller et al, 1995). Dorsolateral pontine activation is seen with PET in spontaneous episodic (Afridi et al, 2005a) and chronic migraine (Matharu et al, 2004a) and with nitroglycerin-triggered attacks (Afridi et al, 2005b; Bahra et al, 2001). These areas are active immediately after successful treatment of the headache but are not active interictally (Figure 3-1). The activation corresponds with the brain region that Raskin and colleagues (1987) initially reported to cause migraine-like headache when stimulated in patients with electrodes implanted for pain control. Similarly, Welch and colleagues (2001) have noted excess iron in the PAG of patients with episodic and chronic migraine, and chronic migraine can develop after a bleed into a cavernoma in the region of the PAG or with a lesion of the pons. What could dysfunction of these brain areas lead to?

Animal experimental studies of sensory modulation. It has been shown in the experimental animal that stimulation of nucleus locus coeruleus, the main central noradrenergic nucleus, reduces cerebral blood flow in a frequency-dependent manner (Goadsby et al, 1982) through an $\alpha_2$-adrenoceptor–linked mechanism. This reduction is maximal in the occipital cortex. In addition, the main serotonin-containing nucleus in the brain stem, the midbrain dorsal raphe nucleus, can increase cerebral blood flow when activated (Goadsby et al, 1991). Furthermore, stimulation of PAG will inhibit sagittal sinus–evoked trigeminal neuronal activity in cat, while blockade of P/Q-type voltage-gated $Ca^{2+}$ channels in the PAG facilitates trigeminovascular nociceptive processing (Knight et al, 2002) with the local GABAergic system in the PAG still intact.

Electrophysiology of migraine in humans. Studies of evoked potentials and event-related potentials provide some link between animal studies and human functional imaging (Giffin and Kaube, 2002). Authors have shown changes in neurophysiological measures of brain activation, but there is much discussion as to how to interpret such changes (Schoenen et al, 2003). Perhaps the most reliable theme is that the migrainous brain does not

KEY POINTS:

- The concept that trigeminovascular nociceptive information comes by way of the most caudal cells provides an anatomical explanation for the referral of pain to the back of the head in migraine.
- Triptans influence the CGRP promoter and regulate CGRP secretion from neurons in culture.
- Human imaging studies have confirmed activation of thalamus contralateral to pain in acute migraine.
- Orexinergic neurons in the posterior hypothalamus can be both pronociceptive and antinociceptive, offering a further possible region whose dysfunction might involve the perception of head pain.

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habituate to signals in a normal way. Similarly, contingent negative variation, an event-related potential, is abnormal in migraineurs compared with controls (Schoenen and Timsit-Berthier, 1993). Changes in contingent negative variation predict attacks, and preventive therapies alter or normalize such changes.

WHAT IS MIGRAINE?

Migraine is an inherited, episodic disorder involving sensory sensitivity. Patients report throbbing pain in the head, but no reliable relationship exists between vessel diameter and the pain or its treatment. Patients report discomfort from normal lights and the unpleasantness of routine sounds. Some mention that otherwise acceptable odors are unpleasant. Normal movement of the head causes pain, and many mention a sense of unsteadiness as if they have just stepped off a boat, despite having been nowhere near the water!

The anatomical connections of, for example, the pain pathways are clear; the ophthalmic division of the trigeminal nerve subserves sensation within the cranium and explains why headache is typically expressed as pain in the frontal region of the head, and the maxillary division is facial pain. The convergence of cervical and trigeminal afferents explains why neck stiffness or pain is so common in primary headache. The genetics of channelopathies is opening up a plausible way to think about the episodic nature of migraine. However, where is the lesion, and what is actually the pathology?

If one considers what patients say, then perhaps they provide the answer to these questions. Migraine aura cannot

Figure 3-1 Positron emission tomography (PET) images from patients with chronic (Matharu et al, 2004a) and episodic (Afridi et al, 2005a) migraine demonstrating consistent activation of the dorsolateral pons as seen in glyceryl trinitrate triggered migraine. Migraine with any frequency shares a unique pattern of brain activation with a crucial aspect of the pathophysiology being located in the brain stem.

Afridi SK, Giffin NJ, Kaube H, et al. A positron emission tomographic study in spontaneous migraine. Arch Neurol 2005a;62:1270–1275. Reprinted with permission. Copyright © 2005, American Medical Association. All rights reserved.

Matharu MS, Bartsch T, Ward N, et al. Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. Brain 2004a;127:220–230. Reprinted with permission of Oxford University Press.

KEY POINTS:

- Functional brain imaging with positron emission tomography has demonstrated activation of the dorsal midbrain, including the periaqueductal gray, and in the dorsal pons, near the locus coeruleus, in studies during migraine without aura. Dorsolateral pontine activation is seen with positron emission tomography in spontaneous episodic and chronic migraine and with nitroglycerin-triggered attacks.

- Migraine is an inherited, episodic disorder involving sensory sensitivity.

- The anatomical connections of the pain pathways in migraine are clear; the ophthalmic division of the trigeminal nerve subserves sensation within the cranium and explains why the top of the head is headache; and the maxillary division is facial pain.
be the trigger for there is no evidence at all after 4000 years that it occurs in any more than 30% of migraine patients. Aura can be experienced without pain at all and is seen in the other primary headaches. There is no photon of extra light that migraine patients receive over others, so for that symptom, and phonophobia and osmophobia, the basis of the problem must be abnormal central processing of a normal signal. Perhaps electrophysiological changes in the brain have been mislabelled as hyperexcitability, whereas dishabituation might be a simpler explanation. If migraine were basically an “attentional” sensory problem with changes in cortical synchronization (Niebur et al, 2002), hypersynchronization (Angelini et al, 2004), all its manifestations could be accounted for in a single overarching pathophysiological hypothesis of a disturbance of subcortical sensory modulation systems (Goadsby, 2003). While it seems likely that the trigeminovascular system and its cranial autonomic reflex connections, the trigeminal-autonomic reflex (May and Goadsby, 1999), act as a feed-forward system to facilitate the acute attack, the fundamental problem in migraine is in the brain. Unravelling its basis will deliver great benefits to patients and considerable understanding of some very fundamental neurobiological processes.

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