16 Mechanisms of Migraine and Its Treatment

Lars Edvinsson[1] · *Antoinette Maassen van den Brink*[2] · *Carlos M. Villalón*[3]
[1]Lund University Hospital, Lund, Sweden
[2]Erasmus University Medical Center, Rotterdam, The Netherlands
[3]Cinvestav-Coapa, México, DF, Mexico

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Abstract: Migraine is characterized by recurrent unilateral headaches, accompanied by nausea, vomiting, photophobia, and/or phonophobia, and in some cases facial symptoms. Current theories suggest that the initiation of a migraine attack involves a primary CNS event, putatively involving mutations in ion channels that render the individuals more sensitive to environmental factors, resulting in a wave of cortical spreading depression when the attack is initiated. Early positron emission tomography (PET) suggested the involvement of a migraine active region in the brainstem. In migraine attacks, data suggest that the pain is associated with the activation of the trigeminal nerve and the release of calcitonin gene-related peptide (CGRP) from the trigeminovascular system. Administration of triptans (5-$HT_{1B/1D}$ receptor agonists) causes the headache to subside and the levels of CGRP to normalize. Administration of CGRP receptor antagonists aborts the headache by specifically blocking the CGRP receptors located within the trigeminovascular system. Modern acute migraine therapy involves modulation of both CGRP and 5-$HT_{1B/1D}$ receptors.

Introduction

Migraine headaches are ascribed as neurovascular disorders that world-wide afflict up to 15–20% of the general population and with a considerable impact on productivity and quality of life. Migraine is characterized by attacks of moderate to severe headache that last for 4–72 h, often unilateral, pulsating, and associated with photophobia/phonophobia and/or nausea/vomiting (Olesen et al. 2006). In migraine with aura, the headache is preceded by transient focal neurological symptoms, most often contralateral to the pain (Goadsby et al. 2002).

Although the exact causes of the primary headaches remain unknown, some pieces of the pathophysiological puzzle are starting to fall into place, particularly after a series of elegant positron emission tomography (PET) studies (May and Goadsby 1999). During the last 20 years, there has been a heated debate whether the primary headaches are neurogenic or vascular in origin. However, molecular and functional studies suggest a way to incorporate the different aspects into an integrated hypothesis as neurovascular headaches (Goadsby et al. 2002; Pietrobon and Striessnig 2003; Edvinsson and Uddman 2005).

In susceptible individuals, changes in environmental or physiological states trigger the migraine headache attack. Migraine susceptibility is linked to mechanisms regulating central sensitization. The systems that govern neuronal excitability involve homeostatic mechanisms and intracellular signaling pathways. The demonstration of mutations in the calcium channel gene CACNA1A, in approximately 50% of families suffering from familial hemiplegic migraine (FHM), suggests that there is also a molecular genetic cause of the more common types of migraine (Ophoff et al. 1996; Terwindt et al. 1998). However, the central nervous system (CNS) is devoid of sensory pain receptors and intracranially only blood vessels in the dura mater and the circle of Willis are supplied with sensory nerves and receptors that can respond to thermal, mechanical, or distension stimuli (Ray and Wolff 1940; Olesen et al. 2006).

Where Does the Attack Start?

In the Brain?

On the basis of the original cerebral blood flow studies, early researchers suggested that migraine is a disease comprised of two main subtypes, migraine with aura and migraine

without aura. In the former, the aura is characterized most often by visual field disturbances, but sometimes also by additional somatosensory disturbances. In three spontaneous attacks of migraine with aura that were captured within 20 min of the onset of visual symptoms, blood oxygenation level dependent (BOLD) data revealed increases in the amplitude of the MR signal (Hadjikhani et al. 2001). A plausible explanation for the blood flow changes seen in association with the aura in a migraine attack is that they are the result of spreading depression – a transient marked reduction in electrical activity in the grey matter, which advances across the cortical surface. The rate of advance is consistent with the spread of symptoms observed and is associated with decreases in blood flow (Lauritzen 1994). One conclusion raised from these studies is that the migraine aura is not evoked by ischemia, but evoked by aberrant firing of neurones and related cellular elements. Probably, the genetic background can make a migraine patient more prone to alterations in the intracranial circulation, since with certain mutations (as seen in FHM) ion channels may be more easily activated (due to altered membrane potential and/or function) and result in excitation of neurons in situations where they are exposed to excessive stress.

An important question is how the event is linked to activation of the trigeminovascular reflex (McCulloch et al. 1986). One tempting way would be to link the cortical spreading depression to neurogenic inflammation in the dura mater and from there activation of sensory and autonomic reflexes (Bolay et al. 2002). However, the dura mater is an extracerebral structure, separated from the brain by, for example, CSF and pial and arachnoid connective tissues; it is nourished by the external carotid artery (Olesen et al. 2006). Alternatively, specific cell bodies projecting from the brainstem to cerebral vessels, such as the extensive adrenergic and serotonergic efferent nerve fibers from neurons in the locus ceruleus and from the raphe nuclei, respectively, could be involved. In fact there are some anatomical data to support this suggestion (Edvinsson et al. 1983; Bradley et al. 2002) showing a close association between intracerebral nerve fibers and cerebral blood vessels.

In patients with migraine without aura, the situation is somewhat more intricate (Weiller et al. 1995). During attacks, small increases in blood flow were observed in the cingulate, auditory and visual association cortices, and in brainstem regions. These changes (except in the brainstem) normalized after injection of sumatriptan and induced complete headache relief. However, the changes were small and could only be significant if the PET data from all nine subjects were normalized, thus being in agreement with previous negative studies with the ^{133}xenon method that lacks the precision of PET (Olesen et al. 1990). Further support for the importance of a brainstem region was obtained in a patient that developed a migraine attack without aura after glyceryl trinitrate administration. Bahra and colleagues (Bahra et al. 2001) observed activation in the dorsal rostral brainstem region and hence reproduced the data seen previously by Weiller and colleagues (Weiller et al. 1995). In addition, the authors observed a neuronally driven vasodilatation and activation of regions associated with pain processing (Weiller et al. 1995; Bahra et al. 2001). During acute attacks, increased local blood flow was observed in brainstem regions (specifically midbrain and pons). The brainstem activation persisted after injection of sumatriptan. These findings suggest that the pathogenesis of migraine (and the associated emesis) involves an imbalance in the activity of brainstem nuclei regulating nociception and vascular control. On the other hand, it could equally well be an activation of the periaqueductal grey area (PAG) acting as a filter to inhibit the pain (Fields and Basbaum 1994). The study revealed activation of the dorsal raphe nucleus (DRN) and the locus ceruleus (LC). Indeed, these centers have a dense supply of serotonergic and adrenergic fibers, respectively, which may evoke vasoconstriction (via catecholamines or 5-HT) and hence

explain the connection with the trigeminovascular reflex. Alternatively, the DRN and LC may send descending fibers to the trigeminal nucleus caudalis (TNC) and dorsal root ganglia where they act in a gate-control function and the PAG acts to inhibit this. Thus, sensory transmission associated with the TNC appears to be regulated by a complex system. It is still unclear whether the brainstem findings reveal the origin of the disease or if it is an accompanying activation designed to limit the symptoms of the migraine headache.

In the Dura Mater?

Application of individual peptides on the dura results in no meaningful activation of cells in the TNC region (Levy et al. 2005), while the application of the "inflammatory soup" causes activation and increased c-fos immunoreactivity (Burstein et al. 1998; Hoffmann et al. 2009). Thus, massive stimulation of the Aδ- and C-fibers in the dura mater may elicit a neuronal response in the brainstem while more normal doses of the agonists do not. Does this ever occur in the clinical situation? The systemic administrations (intravenous) of the above molecules as well as of other vasoactive compounds tested in the "migraine model" by the Danish group have basically revealed that CGRP, PACAP, nitric oxide (nitroglycerine), histamine, sildenafil, and alcohol, inter alia, elicit a weak transient headache in both healthy volunteers and migraine patients, but in a proportion of migraineurs also a more pronounced headache with a maximum at 2–4 h after the drug administration (Olesen 2008). Recent studies of administrations of, e.g., prostacyclin (Wienecke et al. 2010), prostaglandin E_2 (Wienecke et al. 2009), carbachol (Schytz et al. 2010), and VIP/PACAP (Rahmann et al. 2008; Schytz et al. 2009) show the early headache and increases in superficial temporal artery diameter, and some of them a mild late headache resembling "migraine-like." When comparing the headache intensity with that of genuine attacks (Linde et al. 2006), the induced attacks are relatively mild. It is hypothesized that these agents cause their headache effect via the endothelium, mediated by the release of nitric oxide (Olesen 2008). However, it is well known that they use many different other signaling pathways. It is perhaps more reasonable to suggest that the change in vessel tone may excite differently the perivascular sensory nerve fibers to signal dromically to the TG and the TNC.

Nerves in the Walls of Intracranial Blood Vessels

Since intracranial blood vessels are the only source for eliciting intracranial pain (Ray and Wolff 1940), the understanding of the vascular supply by autonomic and sensory nerves is a prerequisite for the understanding of intracranial pain as it occurs in primary headaches. Intracranial blood vessels are supplied with nerve fibers that emanate from cell bodies in ganglia belonging to the sympathetic, parasympathetic, and sensory nervous systems (Gulbenkian et al. 2001). In addition, cerebral resistance vessels may be innervated by fibers that originate within the brain itself, thereby representing an intrinsic nerve supply (Edvinsson and Krause 2002).

Cerebrovascular Autonomic Nerves

The sympathetic nerves (storing noradrenaline and neuropeptide Y) supply the cerebral blood vessels with perivascular adrenergic nerves that arise from the ipsilateral superior cervical

ganglion (Nielsen and Owman 1967), while some nerve fibers that supply the vertebral and basilar arteries originate from the inferior cervical ganglion and the stellate ganglion (Arbab et al. 1988). The activation of these fibers results in vasoconstriction, modulation of cerebrovascular autoregulation, reduction of intracranial pressure, and a decrease in cerebral blood volume and cerebrospinal fluid production (Edvinsson and Krause 2002).

The "classical" neurotransmitter in parasympathetic nerves is acetylcholine (ACh) and their cell bodies contain acetylcholinesterase (AChE). Cerebral blood vessels have perivascular nerves that display AChE activity (Edvinsson et al. 1972; Hara et al. 1985; Suzuki et al. 1990). In several species, ACh induces constriction of isolated cerebral arteries without endothelium, while transmural nerve stimulation predominantly induces relaxation in the same preparations (Lee 1980). The neurogenic vasodilatation in these preparations is not blocked by atropine and is thus non-cholinergic (Lee 1980, 1982). Hence, additional substances may be released together with ACh to mediate dilatation (Lee 1980, 1982; Saito et al. 1985), including VIP, pituitary adenylate cyclase activating polypeptide (PACAP), and nitric oxide (NO), which produce cerebral vasodilatation in vitro and in vivo (Uddman et al. 1993; Jansen-Olesen et al. 1994; Goadsby et al. 1996). In fact, NO might be the last link in cholinergic transmission. Another possibility may be that ACh mainly acts prejunctionally to inhibit neurotransmitter release from the adrenergic nerves (Edvinsson et al. 1977; Lee 2000). The vast majority of parasympathetic nerve fibers to cerebral vessels originates in sphenopalatine and otic ganglia (Suzuki et al. 1988; Edvinsson et al. 1989).

Sensory Nervous System

Most sensory fibers to cranial structures derive from the trigeminal ganglion. In the human trigeminal ganglion, CGRP-immunoreactive neurones occur in high numbers (40% of all neuronal cells) whereas SP-immunoreactive neurones are less numerous (18%). In situ hybridization has revealed that 40% of all nerve cell bodies contain CGRP and CGRP mRNA (Edvinsson et al. 1998a; Tajti et al. 1999). CGRP and SP are potent vasodilators in vivo and in vitro, the former being 10–1,000 times more potent (Edvinsson et al. 1981; McCulloch et al. 1986; Edvinsson et al. 1987; Jansen et al. 1991). Several studies have suggested that SP is involved in plasma extravasation from postcapillary venules in the dura mater during primary headaches (Markowitz et al. 1987). While neurokinin receptor antagonists are potent inhibitors of neurogenic inflammation (Shepheard et al. 1993; Shepheard et al. 1995; Phebus et al. 1997), they were ineffective in the acute treatment of migraine (Goldstein et al. 1997). Furthermore, while CGRP is released during the headache phase of a migraine attack, SP is not (Goadsby et al. 1990; Goadsby and Edvinsson 1993). In addition, SP is now considered not to be involved in vascular nociception in humans (Holthusen et al. 1997). This view is supported by intravital microscopy studies demonstrating that vasodilatation during perivascular stimulation of the middle meningeal artery in vivo was blocked by a CGRP antagonist, but unaffected by neurokinin agonists or antagonists (Williamson et al. 1997). Immunocytochemistry has revealed the expression of PACAP not only in parasympathetic but also in sensory ganglia (Moller et al. 1993; Tajti et al. 1999), suggesting that PACAP may act as a neuromodulator in the sensory systems (Moller et al. 1993). There is a moderate supply of PACAP immunoreactive nerve fibers in the cat cerebral circulation (Uddman et al. 1993). In the rat, the majority of the PACAP-containing fibers around cerebral blood vessels originates in the sphenopalatine ganglion (Edvinsson et al. 2001). In the human trigeminal ganglion,

PACAP-containing cell bodies are more numerous than in laboratory animals, amounting to 15–20% (Tajti et al. 1999). Double immunostaining has revealed that PACAP co-localizes with CGRP in some cell bodies in the trigeminal ganglion. PACAP dilates cerebral arteries and can increase cerebral blood flow (Uddman et al. 1993; Jansen-Olesen et al. 1994; Seki et al. 1995). Activation of the trigeminovascular system results in co-release of CGRP and PACAP into the cat jugular vein (Zagami et al. 1990), a model used in studies of migraine (Goadsby et al. 1988). It is also possible that PACAP may participate in antidromic vasodilatation following activation of the trigeminal vascular reflex (McCulloch et al. 1986).

NO has been suggested as an important molecule for initiation of migraine attacks (Olesen et al. 1995). The expression of NOS in trigeminal nerve cell bodies supports this suggestion. NO released from the endothelium (eNOS), from perivascular nerves (nNOS), or inducible NOS (iNOS) may activate the guanylate cyclase system in smooth muscle cells. This results in a decrease in the local intracellular Ca^{++} level, giving rise to vasodilatation, which may activate the pain sensitive structures around the cranial vessels (Olesen et al. 1995). Few trigeminal neurones express NOS in animals (Nozaki et al. 1993; Edvinsson et al. 1998b; Edvinsson et al. 2001), while the human trigeminal ganglia has about 15% of the cell bodies containing NOS (Tajti et al. 1999). Double immunostaining of the cat trigeminal ganglion has revealed that only few CGRP neurones (less than 5%) are NOS positive (Edvinsson et al. 1998b). The relative functional role of CGRP and NO in the trigeminal ganglion has been studied in the cat; CGRP blockade markedly attenuates the cerebral blood flow increase following trigeminal nerve activation while NOS blockade was without effect (Edvinsson et al. 1998b). On the other hand, activation of the parasympathetic nerves results in a NO-dependent flow increase (Goadsby et al. 1996), suggesting a physiological role for NO in the parasympathetic vasodilator system.

Release of Neurotransmitters in Migraine

During migraine attacks, there is a marked increase in the plasma levels of CGRP in the external jugular vein (Goadsby et al. 1990). At the same time, there is no change of CGRP in peripheral blood or in the levels of NPY, VIP, or SP in the jugular vein (*Table 16.1*). Furthermore, there is no difference between migraine with aura or migraine without aura, as both result in substantial increases in venous CGRP levels at the same time as the patients exhibit pain

Table 16.1
Overview of changes in perivascular neuropeptide levels occurring in acute attacks of primary headache disorders

	NPY	VIP	Substance P	CGRP
Migraine without aura	±0	±0	±0	↑
Migraine with aura	±0	±0	±0	↑
Trigeminal neuralgia	±0	±0	±0	↑
Cluster headache	±0	↑	±0	↑
Chronic paroxysmal headache	±0	↑	±0	↑

±0, no change from before headache, ↑ significant increase in neuropeptide level

(Goadsby et al. 1990; Goadsby and Edvinsson 1993; Gallai et al. 1995). Even when blood samples were taken from the cubital fossa vein, increased CGRP levels in migraine patients were observed, both outside attacks (Ashina et al. 2000) and after nitroglycerine-induced attacks (Juhasz et al. 2003). Triptans have been demonstrated to normalize the CGRP levels in spontaneous (Goadsby and Edvinsson 1993; Stepien et al. 2003) as well as triggered (Juhasz et al. 2005) migraine attacks. The mechanisms behind this reduction in elevated plasma CGRP in humans may be due to the presence of 5-HT_{1B} and 5-HT_{1D} receptors expressed on the trigeminal ganglion cells and fibers (Longmore et al. 1997; Hou et al. 2001), which may, during stimulation, cause inhibition of sensory nerve activity (Wang et al. 2010). CGRP analysis is notoriously difficult in biological fluids and negative studies have appeared, however (Friberg et al. 1994; Tvedskov et al. 2005). This may simply reflect that the methodology of analysis, including the use of HPLC fractionation and rapid cool-centrifugation and freezing of the samples, is crucial as evident from several studies (Edvinsson 2004). Recently, it was verified that saliva also can be used to demonstrate the relation between headache attacks and CGRP release; interestingly a CGRP elevation predicted a positive effect of a triptan (Cady et al. 2009). The reason why SP is not released in migraine might be due to a much lower level of SP than of CGRP within the trigeminovascular system to the intracranial vasculature. Direct electrical stimulation of the trigeminal ganglion in humans, however, results in co-release of CGRP and SP (Goadsby et al. 1988), possibly because here the entire sensory system to the head is activated.

Central Mechanisms in Migraine

Once the trigeminovascular reflex is initiated, resulting in an antidromic activation that involves release of CGRP, the central part of this pathway, the TNC, and/or its reciprocal parts at the C1 and C2 levels are also activated. Experiments in laboratory animals as well as in humans have shown that direct stimulation of either the superior sagittal sinus or the trigeminal ganglion results in activation of cells in this region (Goadsby and Zagami 1991; Goadsby and Edvinsson 1994).

How Is the Trigeminovascular Reflex Initiated?

Following the identification of the trigeminal vascular pathway and its dependence on neuropeptides (Uddman et al. 1985), functional studies showed that denervation does not alter the regional cerebral blood flow or cerebral metabolism, the cerebral vascular responses to carbon dioxide or autoregulation (Edvinsson and Krause 2002). However, vasoconstrictor responses elicited by noradrenaline (McCulloch et al. 1986), alkaline pH, $PGF_{2\alpha}$, $BaCl_2$, subarachnoid blood, or capsaicin are modified (Edvinsson et al. 1990; Edvinsson et al. 1995). The general picture is that following denervation there is no alteration in the maximum contractile response to either of the above agents, but the time to return to the initial basal tone is markedly prolonged. It is hypothesized that vasoconstriction triggers an antidromic release of the sensory neuronal messengers, which results in normalization of the vascular tone. Subsequent studies using antagonists in combination with denervation have shown that CGRP has a significant role in this response (Edvinsson et al. 1995; Edvinsson et al. 1990). Vasodilatation of cortical arterioles induced by acidic pH is not modified by trigeminal

denervation (Edvinsson et al. 1995). Thus, if the primary headache attack involves cortical spreading depression with subsequent vasoconstriction of cerebral vessels, the trigeminal vascular system may have a counter-balancing effect designed to normalize cerebrovascular tone. The activation of this system is noted clinically as an increase in cranial venous outflow of CGRP during the attacks (Goadsby et al. 1988; Goadsby et al. 1990; Goadsby and Edvinsson 1993). In an experimental study of spreading depression, it was demonstrated that CGRP is in part involved in the local dilatation (Wahl et al. 1994). In contrast, spreading depression per se in monkeys did not result in enhanced jugular venous CGRP levels (Piper et al. 1993), which agrees well with patient data (Kruuse et al. 2010). If the patient is in a "latent period" (Fanciullacci et al. 1995), then the spreading depression may induce a strong reflex vasoconstriction that may activate the trigeminovascular reflex (McCulloch et al. 1986) as observed in acute primary headaches (Fanciullacci et al. 1997). The connection may be either functional as suggested by Bolay (Bolay et al. 2002) or anatomical (Cohen et al. 1996).

What Is the Role of the Trigeminocervical Complex?

The nociceptive input from cerebral blood vessels and the dura mater to the first synapse in the brainstem is transmitted by small-diameter Aδ- and C-fiber afferents in the ophthalmic division of the trigeminal nerve via the trigeminal ganglion to nociceptive second-order neurons to the superficial and deep layers of the medullar dorsal horn of the trigeminocervical complex (Liu et al. 2004; Liu et al. 2008). This system extends from the trigeminal nucleus caudalis to the C2–C3 segments. To understand the pathophysiology of primary headaches, it is essential to identify the human brain regions that may process the signs of the disorder. Indeed, there is a rich supply of SP-immunoreactive fibers in the marginal layer and in the substantia gelantinosa of the subnucleus caudalis of the TNC and the Rexed's lamina I and II of the C1 and C2 segments of the human spinal cord (Uddman et al. 2002). In addition, there is a moderate supply of CGRP and PACAP fibers in these areas while NOS or VIP fibers were not seen (Christiansen et al. 2003).

Migraine attacks involve changes that are characterized by pain and nausea, symptoms that are mediated by the sensory system and by centers in the brainstem. The vascular components of the disorder are mediated via the trigeminal nerve. Mechanical or electrical stimulation of the dura mater or of cranial blood vessels reproduces signs of migrainous pain (Ray and Wolff 1940). The central structures that process craniovascular pain have been mapped to some degree. Electrical stimulation of the cat superior sagittal sinus leads to increased metabolic activity in the TNC and in the C2 region of the spinal cord (Goadsby and Zagami 1991). A marked increase of the immediate early gene c-fos in lamina I and II of the TNC and in the superficial layers of the C1 and C2 regions can be seen upon stimulation of the middle meningeal artery, the superior sagittal sinus, or the trigeminal ganglion in monkeys and cats (Kaube et al. 1993; Goadsby and Hoskin 1997; Hoskin et al. 1999). However, the expression of neuropeptides in the brainstem is unaltered during 2 h of superior sagittal sinus stimulation (Christiansen et al. 2003). The c-fos response is reduced by antimigraine drugs such as triptans (Knyihar-Csillik et al. 1997, 2000). In humans, evidence for a central site of action of the triptans has come from binding studies that demonstrate their association with the superficial lamina of the caudal part of the TNC and the cervical dorsal horn as well as of the nucleus of the tractus solitarius. In an attempt to characterize the receptors involved, it has been suggested that 5-HT_{1B} receptors are present in very low concentrations in all these nuclei in humans

(below 12% of total specific binding), while 5-HT_{1D} receptors account for about 50% of the total specific sumatriptan binding (Longmore et al. 1997). In addition, a significant amount of 5-HT_{1F}-binding sites can be seen (Castro et al. 1997; Pascual et al. 1996). The 5-HT_{1F} site has been examined using the specific agonist LY334370 (Shepheard et al. 1999). This agonist had no contractile effect nor did it inhibit CGRP release. Interestingly, it has recently been suggested that inhibition of another 5-HT receptor, the 5-HT_7 receptor, may partially reduce CGRP release (Wang et al. 2010). These data imply that the antimigraine actions could in part be exerted centrally on these nuclei. In humans, the immunocytochemical distribution of CGRP, SP, and PACAP coincides with the reported localization of the 5-$HT_{1B/1D}$ binding sites in the TNC and in particular with the distribution of 5-$HT_{1B/1D}$ receptor (Uddman et al. 2002). Thus, it is tempting to suggest that if the triptans can reach the TNC and the C1 and C2 spinal segments, they may also inhibit the central activity of the sensory trigeminal fibers.

Treatment Aspects: Where Do the Triptans and CGRP Antagonists Act?

As discussed above, triptans may display a central action via 5-HT_{1D} or 5-HT_{1F} receptors. Second, their therapeutic action could be mediated via the inhibition of neuropeptide release from perivascular nerve endings (5-HT_{1D} receptors). Finally, triptans could, in agreement with the concept of their development, mediate their antimigraine effects via a direct vasoconstrictor action at 5-HT_{1B} receptors (for review see Goadsby et al. 2002). Similarly, for CGRP receptor antagonists several putative modes of action have been described. Interestingly, in comparing the clinical effects, it is remarkable that both telcagepant and olcegepant required substantially higher plasma concentrations relative to their in vitro pA_2 to achieve clinical efficacy for the acute treatment of migraine (Olesen et al. 2004; Ho et al. 2008). For example, plasma concentrations of telcagepant associated with clinical efficacy are in the micromolar range, which is substantially higher than the pA_2 that we have seen for the cranial vascular effect (in the nanomolar range). Several factors may account for these apparent discrepancies. First, a high protein binding of these compounds; indeed, a considerable protein binding is suggested by the fivefold reduction of the potency of telcagepant in the presence of serum (Salvatore et al. 2008). Second, a concentration of drug equal to the pA_2 value may not be sufficient to decrease functional responses since it only shifts the concentration response curves twofold to the right; most likely, a concentration of a least ten times the corresponding pA_2 would functionally inhibit relaxations to CGRP. Thirdly, as nerve terminals releasing CGRP are located in the adventitia close to the media layer of the blood vessels, the concentration of telcagepant at the receptors may be substantially smaller than that at the lumen of the blood vessel, that is, the plasma concentration. This phenomenon is unlikely to occur in vitro, where the antagonist can reach the CGRP receptors from both the luminal and abluminal sides. Lastly, the therapeutic effect of CGRP receptor antagonists could also be mediated via pathways other than only blockade CGRP-induced vasodilatation. Penetration of telcagepant through the blood-brain barrier may be necessary in addition to the peripheral blockade to achieve antimigraine efficacy (Edvinsson 2008). Arguments in favor of a neuronal mechanism are the lack of presynaptic CGRP receptors in the meninges, which suggests that exogenous CGRP is unlikely to directly modify the innervating sensory nerve fibers (Lennerz et al. 2008). This finding is also in agreement with in vivo data obtained in rats, suggesting that an action of CGRP on the dura mater cannot account for the activation of peripheral afferents during migraine

(Levy et al. 2005). In this study, the effects of CGRP in the meninges, including meningeal vasodilatation, were not sufficient to activate or sensitize meningeal nociceptors. Clearly, further studies are needed to resolve the therapeutic mechanisms involved in CGRP receptor antagonism.

Summary

Current data provide a model in which a central "generator" or an "active region" (different in migraine and in cluster headache) is activated. Following changes in cerebral vascular tone, the trigeminovascular reflex is initiated to counter-balance cerebrovascular constriction in part via release of CGRP and VIP. The study of neuropeptide levels in migraine and cluster headache provides a link between the clinical and the basic research, work that is crucial for the understanding of migraine pathophysiology. Indeed, plasma concentrations of CGRP, but not of other neuropeptides, are elevated during migraine headache (with and without aura) and these are normalized by triptans in parallel with alleviation of headache.

The activation of TNC provides the central link to nociception, pain development, and associated symptoms. Hypothetically, intense activation of central pain pathways may involve the superior salivatory nucleus, resulting in parasympathetic VIP release, and manifestation of additional facial symptoms in, for example, cluster headache. A number of possibilities to interact with the sensory system have recently been shown. It was reported that an adenosine A_1 receptor agonist acts prejunctionally to inhibit sensory neurogenic vasodilatation, CGRP release, and firing of second-order neurones in the TNC (Honey et al. 2002). Its clinical usefulness is now evaluated.

By blocking CGRP receptors postjunctionally, the recently developed CGRP blockers (Edvinsson et al. 2002; Salvatore et al. 2008) have been found to be effective in the acute treatment of migraine (Olesen et al. 2004; Ho et al. 2008). Thus, both in spontaneous cases of migraine and in headache attacks induced by administration of CGRP, the CGRP receptor antagonists were effective without any noticeable side effects, establishing a new principle in the acute treatment of migraine (Edvinsson 2009; Villalón and Olesen 2009).

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