The Headaches

Third Edition

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CGRP Involvement in Migraines

Lars Edvinsson and Richard Hargreaves

The functional studies crucial to any hypothesis regarding primary (migraine and cluster) headaches rests on the classic observations of Ray and Wolff (1,2), who described painful sensations that resulted from mechanical or electrical stimulation of large cerebral arteries, venous sinuses, and dural arteries. The pain-sensitive supratentorial structures (but not subtentorial elements) are innervated by sensory trigeminal nerve fibers arising from pseudeounipolar sensory neurons with their cell bodies in the trigeminal ganglion. The central projections from these neurons connect into the central nervous system (CNS) at second-order sensory neurons within the brainstem trigeminal nuclei. Uncontrolled studies of retrogasserian rhizotomy of the trigeminal ganglia have been positive for the relief of migraine (2). Antidromic or local mechanical stimulation of sensory nerve endings is known to cause vasodilatation in peripheral vessels via the release of vasoactive materials such as substance P and calcitonin gene-related peptide (CGRP) (3,4). This vasomotor effect of the sensory nerves in the periphery appears to have a counterpart in the cerebral circulation with the trigeminal system. The fibers and the cell bodies contain a number of messengers, but CGRP is the one most frequently expressed (5). Moreover, CGRP, and CGRP released from perivascular nerves in the meninges, has been conclusively demonstrated experimentally to evoke clear vasodilation in pain producing intracranial structures (6–8). The neuroanatomic, neurophysiologic, surgical, and pharmacologic evidence thus point to a key role for the trigeminocerebrovascular system in the transmission of nociceptive information to the CNS during primary headache.

CGRP immunoreactivity associated with intracranial vessels was first shown in 1984 (9), and subsequently found to originate in perikarya within the trigeminal ganglia of all species examined, including humans (10). CGRP is frequently colocalized in trigeminal neurons with other proinflammatory sensory neuropeptides and vasoactive substances. CGRP-containing cells are the most prevalent phenotype in the trigeminal ganglion (5). Four sources of cerebrovascular CGRP have been described: (i) the ophthalmic division of the trigeminal ganglion, to innervate the circle of Willis and its branches by the nasociliary nerve; (ii) the maxillary division, probably via an extradural branch at the skull base to the internal carotid artery; (iii) the internal carotid miniganglia, via the greater deep petrosal nerve to distribute in the internal carotid artery and distribute proximally in its intracranial ramifications; (iv) in the upper cervical dorsal root ganglia (C_1 to C_3) to innervate the caudal third of the basilar artery and the vertebral artery (6,10–18). The major cerebral arteries (anterior, middle, and posterior cerebral arteries, vertebral and basilar arteries) and pial arterioles of the cortical surface are invested with fine varicosed nerve fibers that contain CGRP (19). These nerve fibers are present in the adventitia and at the adventitial-medial border of the blood vessels. CGRP is colocalized in these fibers with substance P (20,21), neurokinin A (22), PACAP (11), NOS (11,23), amylin (24), and nociceptin (25).

CGRP and its receptors are widely expressed in peripheral tissues and the central and peripheral nervous systems and their activation has been linked to a diverse range of biological functions (4,26,27). CGRP is a 37-amino acid peptide that results from tissue-specific alternative splicing of the calcitonin gene (28). It exists in two forms, α- and β-CGRP (29), which show considerable homology with amylin and adrenomedullin. CGRP receptors have a heterodimeric nature comprising a G-protein–coupled (Gs; adenylate cyclase) receptor (GPCR) known as the calcitonin receptor-like receptor (CLR) and a single transmembrane-spanning protein known as receptor activity-modifying protein 1 (RAMP1) (30). RAMP1 can also modulate the pharmacology of other GPCRs such as the calcitonin receptor (CTR), which when coexpressed with RAMP1 shows high affinity for amylin and CGRP (31,32). The receptors for the calcitonin-related peptides, CLR and CTR, are in the same class B family of GPCRs as the receptors for secretin, glucagon, vasoactive intestinal polypeptide (VIP) and parathyroid hormone. Until

recently, the pharmacology and physiology of CGRP receptors could only be investigated using truncated versions of the CGRP peptide (CGRP8-37). However, nonpeptide antagonists have now been developed (33), and these have facilitated exploration of the physiologic role of CGRP. It is noteworthy, however, that marked species differences have been observed in the binding of these antagonists that are important in the interpretation and selection of experimental and clinical pharmacologic models of pathophysiology (34).

The wide distribution of CGRP and its receptors in CGRP the brain and cardiovascular system gives this peptide a potential for diverse physiologic roles in normal and many pathological states (26,35,36), but its most pronounced action is probably that of vasodilatation (4,37). The dense innervation of the cerebral circulation by trigeminal CGRP-containing trigeminal nerve fibers (20,21) is central to its putative involvement in primary headaches. Trigeminal fibers mediate dilatation of brain (19,38–40), meningeal and dural vessels (7,8,40–43), and increases in cerebral blood flow (CBF) (44), yet appear to have no tonic influence on CBF or metabolism (45). Experimentally, these fibers release CGRP when simulated electrically (44,46–49) or chemically by capsaicin (50–52) and when the trigeminovascular reflex is triggered (21,50,53). CGRP clearly has a key functional role (21,50,53,54) in the trigeminovascular system and CGRP containing fibers appear clinically to be activated in primary headaches and in stroke (48,55–59), supporting its role in cranial sensory functions. This review concentrates on the role of CGRP and its receptors within the intracranial vasculature as targets for antimigraine drugs; however, it is recognized that there is a widespread distribution of CGRP receptors within pain pathways in the trigeminal nuclei of the brainstem and that these could be activated by CGRP released from the central terminals of the trigeminal nerves and play a role in nociceptive transmission from headache pain–producing tissues.

NEUROPEPTIDE RELEASE IN PRIMARY HEADACHES

The role of the sensory nerves around the intracranial vessels in primary headaches has been elucidated by analysis of neurotransmitter release in man: Activation of the trigeminal ganglion resulted in unilateral blood flow increases, CGRP and substance P release, and facial flushing on the side of stimulation (46).

Migraine

There are both vascular and neurogenic components to migraine attacks (55). Many consider that the disorder is caused by mutations in a calcium-channel gene rendering neurons unstable and capable of initiating a migraine attack. The evidence for calcium-channel involvement, however, remains best for a relatively rare migraine variant, familial hemiplegic migraine (60). It has been proposed that as a result of this instability, the trigeminovascular system becomes activated during the initiating events in migraine pathophysiology, resulting in an antidromic release of CGRP, vasodilatation of pain-producing intracranial blood vessels, and activation of second-order sensory neurons in the trigeminal nucleus caudalis with subsequent perception of pain. Early clinical studies showed that sensory neuropeptides are released and can be measured in the jugular vein when the trigeminal ganglion is stimulated during lesioning of the trigeminal ganglia for the treatment of trigeminal neuralgia (46). This observation led to the hypothesis that neuronal messenger molecules (neuropeptides) associated with the autonomic and sensory nerves (46) may be similarly released during migraine.

TABLE 31-1 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

The cranial venous outflow from the external jugular vein (Table 31-1) was therefore analyzed for markers of sympathetic (neuropeptide Y [NPY]), parasympathetic (VIP), and sensory (CGRP and substance P) nerves during migraine headache. No changes were observed in the levels of NPY, VIP, or substance P, but a marked increase in CGRP was observed during migraine headache CGRP release was observed in patients with attacks of migraine with aura and those without aura. Two individuals with facial autonomic symptoms similar to those seen in cluster headache (e.g., nasal congestion and rhinorrhea), also showed increased levels of VIP suggesting the additional involvement of the parasympathetic system in these two individuals (56).

The apparently selective release of CGRP rather than substance P has been a point of considerable discussion. Sensory trigeminal C fibers arise from neurons in the trigeminal ganglia in which CGRP and substance P are colocalized, whereas sensory Aδ fibers arise from

trigeminal neurons containing predominantly CGRP with glutamate (10,15,16,61). The detection of CGRP in the venous effluent blood may simply reflect a greater density of innervation of the cerebral circulation or could reflect differential release from C-fiber pools or preferential activation of Aδ- over C-fiber populations. Regardless of its origin, CGRP released in the trigeminovasculature mediates prolonged vasodilatation of these pain-producing intracranial blood vessels. The initial clinical observations have subsequently been confirmed (48,62). Additional evidence supporting a role for CGRP in migraine headache came from the pivotal observation that after dosing the 5-$HT_{1B/1D}$ agonist antimigraine compound sumatriptan, the plasma levels of CGRP returned to normal concomitant with successful amelioration of the headache (48). 5-$HT_{1B/1D}$ receptors are expressed on trigeminal ganglion cells of man (63) and guinea pig (64) and on human trigeminal sensory fibers (65,66), thereby providing sites for presynaptic inhibition of CGRP release from trigeminal sensory nerve terminals. It has been proposed from studies in trigeminal neurons that this sumatriptan–mediated inhibition of CGRP release is through a prolonged 5-HT_{1D} receptor-mediated increase in intracellular calcium (67,68).

Cluster Headache

Cluster headache is a well-described, clear-cut clinical syndrome. Patients with episodic cluster headache, fulfilling the criteria of the International Headache Society (IHS), were examined during acute spontaneous attacks of headache to determine the local cranial release of neuropeptides (57). During the attacks, the blood levels of both CGRP and VIP were markedly raised, although there was no change in NPY or substance P (see Table 31-1). Treatment with oxygen or subcutaneous sumatriptan aborted the pain and normalized the CGRP levels (57). The finding of elevated levels of both CGRP and VIP during attacks suggests that there is activation of a brainstem reflex, the afferent arc of which is the trigeminal nerve and the efferent the cranial parasympathetic outflow from cranial nerve VII (47,69,70). Indeed, it was particularly noteworthy that VIP release was detected in all subjects in line with their extracranial facial parasympathetic symptoms.

The results in idiopathic headaches are in excellent agreement with those of others, who have shown that CGRP levels are elevated during nitroglycerine-elicited attacks of cluster headache (57,71,72) and related to the intensity of the headache pain. There was no alteration in substance P levels. Interestingly, only when the subjects were in an active period was nitroglycerine able to elicit an attack of cluster headache (72), suggesting that the trigeminovascular system maybe hyperreactive at this time.

Trigeminal Neuralgia

No differences have been found in the resting levels of sensory neuropeptides between normal individuals and subjects with trigeminal neuralgia (46). In contrast, stimulation of the trigeminal ganglion during thermocoagulation caused a marked increase in the blood levels of CGRP and substance P that was associated with unilateral facial flushing. After cessation of the stimulation, the peptide levels returned toward normal levels. Other studies of an unstable trigeminal system in which activation of a facial trigger point evoked pain that was associated with rhinorrhea, facial flushing, and elevated levels of CGRP have also highlighted the complex interplay between vascular and pain biology responses to neuronally derived vasoactive peptides such as CGRP in the cranial vasculature (73).

Chronic Paroxysmal Hemicrania

Chronic paroxysmal hemicrania (CPH) is a rare syndrome that is defined by the IHS operational diagnostic criteria as frequent short-lasting attacks of unilateral pain usually in the orbital, supraorbital, or temporal regions that may last for 2 to 45 minutes (attack frequency, often five or more each day). The pain is associated with prominent autonomic symptoms such as conjunctival injection, lacrimation, nasal congestion, rhinorrhea, ptosis, or eyelid edema. According to the diagnostic criteria, the attacks should settle rapidly on treatment with indomethacin. In one such case of CPH, it was observed that, during pain, the CGRP level rose 3 times compared to the level while the subject was on indomethacin. The VIP level increased 4 times during an attack and normalized with indomethacin treatment (74). The case report and the accompanying data show that attacks of CPH are characterized by activation of both sensory and parasympathetic cranial nerve fibers. The changes observed in CGRP and VIP levels during CPH suggest that some aspects of its pathophysiology may resemble those of cluster headache.

RESPONSES TO CGRP

CGRP is a potent cerebral vasodilator in all species studied to date (19). The relative potency of different forms of CGRP varies across species and so care is need in the interpretation and extrapolation of data. In human cerebral arteries, the maximum responses to CGRP, substance P, and neurokinin A are similar, but CGRP induces relaxations at 100 to 1,000 times lower concentrations. In general, CGRP is the most potent known vasoactive constituent of trigeminovascular nerves, by far superseding substance P, neurokinin A, PACAP, amylin, galanin, and dynorphine in efficacy and potency (Table 31-2). In addition, CGRP is about 25-fold more potent as a vasodilator of

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