Chapter 31

CGRP Involvement in Migraines

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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