Neuropeptide effects in the trigemial system – relevance to the pathophysiology of migraine

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The neuropeptides substance P, calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP) have been considered to be important mediators in migraine and other primary headaches. CGRP and VIP have been found at increased concentrations in jugular venous plasma during attacks of migraine or cluster headache, and CGRP receptor antagonists have recently been shown to be effective in migraine therapy. Substance P and CGRP are produced from a subset of trigeminal afferents and VIP from parasympathetic efferents. Release of these neuropeptides in the meninges cause arterial vasodilatation or mast cell degranulation and plasma extravasation. CGRP released from central terminals of trigeminal afferents in the spinal and medullary dorsal horn seems to facilitate nociceptive transmission via a presynaptic mechanism. The central effect of CGRP is substantiated by the suppression of nociceptive c-fos activation and neuronal activity in the spinal trigeminal nucleus following CGRP receptor inhibition. The distribution of immunoreactivity of CGRP receptor components supports these proposed functions and additionally indicates possible CGRP effects mediated by glial CGRP receptors. Infusion of nitric oxide (NO) donors is known to induce delayed headache attacks in migraineurs. The same treatment in rats increased the stimulated CGRP release from isolated trigeminal ganglion and the number of CGRP- and neuronal NO synthase-immunoreactive trigeminal ganglion neurons. The increase in spinal trigeminal activity evoked by NO donors in rat was reversed by CGRP receptor inhibition. The currently available data point to multiple sites of CGRP action in trigeminal nociception and the pathogenesis of migraine.