

DEBATE: CGRP RECEPTOR BLOCKADE IS THE MOST EFFECTIVE TREATMENT FOR MIGRAINE (NO)

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Migraine is one of the complex diseases and the associated symptoms such as nausea, photophobia and photophobia are troublesome as well as the throbbing headache aggravated by motion. Neurobiology of migraine and mechanisms mediating headache have been clearly demonstrated over the last several decades. The trigeminal nerve, its innervation pattern of cranial structures particularly blood vessels and activation of brainstem trigeminal nuclei have fundamental role in development of migraine headache. The initial sensitization and activation of nociceptors in the meninges lead to sensitization of central pain pathways. Though central sensitization depends on input from peripheral pathways at the beginning, it can be maintained independently of peripheral input in later stages. Central sensitization and wind up phenomenon develops through the co-release of substance P & glutamate from trigeminal nerve endings in the dorsal horn of the spinal cord and NMDA receptor activation mediates subsequent events. The inhibition of peripheral trigeminal nociceptive activity at the onset of a migraine attack (mild, throbbing headache) could also abort central sensitization and a full-blown migraine attack.

Trigeminovascular system is also essential in regard to the site of action for pharmaceutical agents such as triptans, ergots, neuropeptide antagonists, and non-steroidal anti-inflammatory drugs (NSAIDs). CGRP is found in small to medium-sized neurons in the trigeminal ganglion and is located in both in perivascular trigeminal sensory nerve endings acting on cranial blood vessels and at the central synapses in the brainstem trigeminal pain nuclei mediating pain signals to higher order cortical areas. Calcitonin gene-related peptide (CGRP) is widely expressed in the nervous systems and related to nociceptive, secretory and vasoactive functions. CGRP administration causes a migraine attack in migraineurs and is released from trigeminal nerve endings during migraine attacks. CGRP is a strong vasodilator in cerebral arteries. Recently developed CGRP receptor antagonists have ability to abort migraine attacks through both peripheral and central signalling mechanisms.

Effectivity of selective CGRP receptor antagonism were first showed by olcegepant, which only be administered intravenously. However its effectivity was not impressive, as olcegepant (2.5 mg) resulted in 66% headache relief after 2 hours, whereas subcutaneous sumatriptan resulted in 81-92% headache relief after 2 hours. Subsequent related compound telcagepant, the first orally bioavailable drug did not make difference, the headache relief was only 55% for telcagepant 300 mg. Based on results from a meta-analysis, initial efficacy of telcagepant is also low compared to triptans, as rizatriptan 10 mg (41%), almotriptan (35%) and sumatriptan (33%) all show better efficacy than that of telcagepant (26%) for pain free at 2 hours.

These results are not unexpected in relation to the site of action of both migraine selective agents. Triptans target serotonergic receptors within the trigeminal nerve fibers surrounding cephalic blood vessels. They display high affinity for 5-HT_{1D} and 1B receptors, and some of them are also agonists at the 5-HT_{1F} receptor. The 5-HT_{1D} and 5-HT_{1F} receptors, located prejunctionally on the peripheral and central ends of sensory trigeminal neurons, hyperpolarize nerve terminals and thereby inhibit trigeminal activation. Triptans inhibit the release of CGRP, as well as other neuropeptides from perivascular nerve endings. Therefore triptans act upstream to CGRP receptor antagonisms and are superior to CGRP receptor antagonisms, since CGRP is not the only player in migraine pathophysiology.

In conclusion, though the effectivity of CGRP receptor antagonists was demonstrated in migraine, those results indicates that CGRP receptor blockade is not the most effective way of aborting a migraine attack.