**CALCITONIN GENE RELATED PEPTIDE: NEW INSIGHT INTO MIGRAINE PATHOPHYSIOLOGY**

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Two theories of migraine pathogenesis have dominated the scientific community for over 300 years. During the 17th century, Willis proposed that migraine pain was due to arterial distension in the meninges. Many people such as Wepfer and Latham popularized this vascular theory. However, other people such as Harvey and Lieving held the view that migraine was a neural disorder and that the pain stemmed from the dysfunction of the nervous system. The discovery of the effectiveness of vasoconstrictors such as ergotamine and most recently triptans further bolstered the vascular theory. However, recent advances in genetics, migraine physiology, and drug development suggest that vascular dilation might not, in fact, be central to the development of migraine pain.

Development of migraine is strongly influenced by genetic factors. First-degree relatives of migraine patients have a 2-4 fold increase in relative risk of having a migraine. It has been suggested that the "migraine brain" is hypersensitive to various internal and external triggers leading to brain activation. During a migraine attack, normal filtering of otherwise innocuous sensations such as light, sound, odor, and touch appears to be deficient. Inputs and sensations become bothersome and occasionally painful. Although CGRP was first discovered as a potent vasodilator, CGRP is now recognized as being widely expressed in both the central and peripheral nervous systems. CGRP and its receptors are expressed in areas of the brain that may be important to migraine pathogenesis such as the hypothalamus, amgydala, periaquductal gray, visual, auditory and olfactory systems as well as the trigeminal nucleus and ganglia.

Telcagepant is a novel, orally available, CGRP receptor antagonist currently in Phase III development for the treatment of acute migraine. It is a highly potent compound with Ki of 0.8nM and IC50 of 2nM. Its CNS penetration is limited by P-glycoprotein (PGP) to 1.3 to 1.6%. Although our initial hypothesis that a peripheral blockade of CGRP would be sufficient for clinical efficacy, Phase II and III data suggest that a much higher dose of 150-300mg is required for clinical efficacy. At these doses, the plasma concentration reaches approximately 2-4 uM level which is a much higher concentration than that expected for peripheral blockade. A study in rhesus monkeys suggested that at this dose, a meaningful CSF concentration relative to the telcagepant's Ki could be achieved despite PGP. This data suggests that peripheral blockade of CGRP is insufficient for acute migraine efficacy and that telcagepant likely acts centrally in order to exert its antimigraine effect. This data is consistent with that for triptans in which the dose required for efficacy is limited partly by CNS side effects of sedation and asthenia.

Also supportive of a key role of the CNS in migraine, several studies have shown that vasodilation may not be necessary for the development of migraine pain. Functional brain imaging studies during migraines with aura have demonstrated that headache pain can start when cerebral blood flow is decreased, that is, when blood vessels are constricted Conversely, headaches sometimes disappear even though cerebral blood flow is increased. Intravenous infusion of vasoactive intestinal peptide (VIP) to migraineurs mediates a marked dilation in cranial arteries, but does not induce a migraine. In addition, sidefanil, a known vasodilator and NO donor is able to induce a delayed migrainous headache in both healthy and migraineurs. The delayed migrainous headache is not associated with vasodilation or neuropeptide increase in peripheral circulation. These findings suggest that although vascular dilation may contribute to some migraine attacks, it does not play a central role in most migraine attacks. In this presentation, we will review the new data that has helped us to gain further insights to this 300-year-old controversy.