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COMMENTARY

Calcitonin gene-related peptide (CGRP) antagonists: blockers of neuronal transmission in migraine

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The neuropeptide calcitonin gene-related peptide (CGRP) is a potent vasodilator that is contained in and released from sensory nerves. CGRP has been implicated in migraine, and the nonpeptide CGRP antagonist BIBN4096BS has been shown to be effective in clinical trials in migraine. To date, it has been largely assumed that the CGRP antagonist is effective due to its ability to block vasodilator activity. Goadsby and co-workers present data that now suggest that CGRP antagonists may also block neuronal transmission in migraine.
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Abbreviations: CGRP, calcitonin gene-related peptide

Calcitonin gene-related peptide, CGRP, is a 37 amino-acid sensory-nerve derived neuropeptide. CGRP was discovered when alternative processing of RNA transcripts from the calcitonin gene was shown to result in the production of distinct mRNAs encoding CGRP (Amara *et al*., 1982). It was soon realised that this peptide was widely distributed in sensory nerves throughout the central and peripheral nervous system. CGRP has a range of biological activities but it is best known for its vasodilator activity, especially at the microvascular level. For example, intradermal injection of picomole amounts into human skin leads to an increased blood flow, which lasts several hours (Brain *et al*., 1985). However, the importance of this peptide in the regulation of blood flow in physiological and pathophysiological situations remains unclear.

Migraine is a common and debilitating primary headache characterised by a unilateral throbbing pain with a range of other symptoms often present (see Goadsby *et al*., 2002). CGRP has been shown to be important in the trigeminovascular system that is known to play an important role in the pathogenesis of migraine headache (see Edvinsson 2003; Olesen *et al*., 2004). It has been known for some time that increased levels of CGRP are detected in samples taken from the draining jugular vein, ipsilateral to the attack (Goadsby *et al*., 1990). This evidence was used at the time to strengthen the hypothesis that migraine involves a sterile neurogenic inflammatory event, especially as treatment with the 5-$HT_{1B/1D}$ agonist sumatriptan causes a decrease in the amount of CGRP detected in animal models of migraine as well as in migraine (Goadsby & Edvinsson, 1993).

The peptide CGRP antagonist $CGRP_{8-37}$ has played an important role in the understanding of CGRP-related mechanisms in animal models of neurogenic vasodilatation (Escott *et al*., 1995). More recently, the only potent nonpeptide CGRP receptor antagonist available to date (BIBN4096BS) has been characterised through use of some of these models (Doods *et al*., 2000). This antagonist is selective for the heterodimer CGRP receptor which is composed of a 7-transmembrane G-protein-linked component (calcitonin receptor-like receptor, CL) and also requires a receptor activity membrane protein (RAMP1) for functional acivity (McLatchie *et al*., 1998). The nonpeptide receptor antagonist BIBN4096BS has been shown to be a selective antagonist for this receptor (Hay *et al*., 2002).

It has been recently revealed that BIBN4096BS has a beneficial effect when given in phase II clinical trials in migraine (Olesen *et al*., 2004). The 5-$HT_{1B/1D}$ agonists now have an important place in the treatment of migraine and the related condition cluster headache, alongside a number of less specific drugs that have more general pain-relieving effects. However, 5-$HT_{1B/1D}$ agonists are used with caution in certain classes of patients with cardiovascular complications, due to the presence of vasoconstrictor 5-$HT_{1B/1D}$ receptors on coronary arteries. In addition, a component of patients suffer a second rebound attack that can be worse than the first attack. Thus, there is a need for new treatments with improved efficacy and side effect profiles and it has been suggested that CGRP antagonists may fit this profile.

The manuscript by Goadsby and co-workers presents results that indicate that CGRP has a role in mediating nociceptive information in the cerebrovascular circulation. Indeed, the present manuscript provides evidence that two CGRP receptor antagonists (BIBN4096BS and $CGRP_{8-37}$) inhibit neurons in the trigeminocervical complex following peripheral activation by stimulation of the superior sagittal sinus and activation by locally applied glutamate. The latter result is indicative of a postsynaptic location. Furthermore, the antagonists were effective when given by local application, suggesting that the site of action must be close to the trigeminocervical complex. This provides further evidence for the antimigraine potential of CGRP antagonists.

While the role of CGRP as a vasodilator is well studied and may contribute to the increased blood flow observed ipsilateral to migraine attacks, less is known about its role as a mediator of nociceptive information. There are several theories that

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have arisen as to the initiation of migraine. The present results are in keeping with the neuronal sensitisation hypo-thesis in migraine that has been proposed by Burstein (2001). This hypothesis interprets migraine in a similar manner to that which has been documented for other pain states, with peripheral and central sensitisation components. CGRP has a wide distribution in the central nervous system (CNS), with evidence for a presence in a range of CNS structures. The clinical effectiveness of the novel CGRP antagonist, BIBN4096BS, potentially represents a significant advance in the treatment of migraine and may offer analgesic efficacy in other pain states. In support of this statement, the peptide antagonist $CGRP_{8-37}$ has been suggested to be analgesic after intrathecal administration (Bennett *et al*., 2000), to influence morphine tolerance (Powell *et al*., 2000) and to modulate hormone release (Li *et al*., 2004). Thus, we may be just beginning an understanding of the potential of CGRP as a pivotal neurotransmitter in pathophysiological situations.

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