LEADING ARTICLE

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Calcitonin Gene-Related Peptide Antagonists as Treatments of Migraine and Other Primary Headaches

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Abstract

Calcitonin gene-related peptide (CGRP) is a potent neuromodulator that is expressed in the trigeminovascular system and is released into the cranial circulation in various primary headaches. CGRP is released in migraine, cluster headache and paroxysmal hemicrania. The blockade of its release is associated with the successful treatment of acute migraine and cluster headache. CGRP receptor blockade has recently been shown to be an effective acute anti-migraine strategy and is non-vasoconstricting in terms of the mechanism of action. The prospect of a non-vasoconstricting therapy for acute migraine offers a real opportunity to patients, and perhaps more importantly, provides a therapeutic rationale to reinforce migraine as a neurological disorder.

Migraine is a common[1] and often very disabling disorder[2] that is increasingly recognised as a neurological condition.[3] Although there is a range of therapies for the acute treatment and prevention of migraine,[4] the serotonin 5-$HT_{1B/1D}$ receptor agonists or 'triptans'[5] stand out in terms of their clinical and neuroscientific impact. Their description as acute anti-migraine compounds,[6] and the subsequent validation of sumatriptan in this regard,[7,8] launched a wave of development that changed the face of migraine in particular, and probably primary headache more generally.

The triptans are considered to be safe[9] and effective.[10,11] However, the triptan development programme left two crucial questions unanswered for the next generation of acute attack treatments. First, are acute anti-migraine drugs necessarily vasoconstricting in their mechanism of action?[12] Secondly, what is the site of action of acute anti-migraine medications? These questions lead us to the next issue, which is whether drug development can move away from the vessel and, thus, jump an important safety hurdle. These questions are not trivial in their scientific impact, are certainly of considerable importance to patients, and may be answered by the use of calcitonin gene-related peptide (CGRP) antagonists.

This review discusses the case for a non-vascular treatment of migraine and primary headache, in the context of CGRP antagonists. The historical development of the CGRP receptor antagonist for the treatment of migraine can be traced from early trigeminovascular studies. This leads to a discussion of CGRP and the trigeminovascular system, illuminated by the interactions of these with the triptans. Finally, the clinical arguments are formulated and

the initial clinical trial data discussed, which suggest that CGRP receptor antagonists are indeed likely to be the next development in the treatment of acute migraine.

1. Historical Perspective

CGRP was first recognised as the product of alternative RNA processing of the *calcitonin* gene.[13] It was reported at a very early stage following its discovery that this product was expressed in the brain.[14] Some years before reports of the existence of CGRP, cranial blood vessels were noted to contain substance P,[15] and because migraine was considered to be a vascular headache,[16] interest developed around this innervation. The study of the innervation of the cranial circulation was accelerated by the fact that substance P was a vasodilator.[17,18] After its discovery, CGRP was quickly recognised to co-exist with substance P in the nerve fibres that innervate blood vessels.[19] However, just prior to the first description of CGRP, it had been shown that substance P played a crucial role in the trigeminal innervation of the meninges. Pial blood vessels were shown to be innervated by substance P-containing fibres from the trigeminal ganglion,[20,21] and stimulation of the pial blood vessels *in vitro* could induce the release of substance P.[22,23] Tracer studies showed that neurons innervating the middle meningeal vessel, a branch of the external carotid artery, were co-localised in the trigeminal ganglion with substance P-like immunoreactivity[24,25] and, similarly, that the cerebral vessel innervation could be traced to the trigeminal ganglion.[26] Moreover, it was clear that dura mater received an important substance P innervation.[23] Thus, substance P was considered first, so-to-speak, in terms of a potential role in migraine,[27] and in many ways this delayed the study of CGRP-related mechanisms in migraine.

From a physiological viewpoint, a key observation that suggested the importance of CGRP over substance P was presented by Edvinsson and colleagues at a Neural Regulation of the Cerebral Circulation meeting[28] and then subsequently more fully in 1986.[29] The authors demonstrated that CGRP was involved in protective mechanisms in the cerebral circulation. Given the background of the study of the trigeminovascular system in terms of craniovascular physiology,[30] it seemed appropriate to this author to study CGRP-related mechanisms in humans. Edvinsson agreed to collaborate on 21 June 1985, the European mid-summer, and the studies were commenced shortly thereafter. The dissection of the pre-eminence of CGRP mechanisms dates from this time as we performed human studies to establish that the direction of the animal work was correct.[31] It soon became apparent that CGRP was a crucial link in the understanding of trigeminovascular activation in migraine,[32] and so the story now unfolds…

2. Calcitonin Gene-Related Peptide (CGRP) and the Trigeminovascular System

Given that the distribution of the pain in migraine is largely in the first (ophthalmic) division of the trigeminal nerve and the cutaneous distribution of the C_2 sensory root, the anatomy and physiology of the trigeminovascular system is reviewed (see figure 1). These data underpin and inform the discussion of CGRP in migraine.

2.1 Anatomy

Surrounding the large cerebral blood vessels, the pial blood vessels, the large venous sinuses and the dura mater is a plexus of largely unmyelinated fibres that arise from the ophthalmic division of the trigeminal ganglion in the posterior fossa[24] and from the upper cervical dorsal roots.[33] This sensory innervation has recently been much better characterised for both an external carotid branch vessel,[34] and for the superior sagittal sinus.[35] Trigeminal fibres innervating cerebral blood vessels arise from neurons in the trigeminal ganglion that contain substance P and CGRP,[19] both of which can be released when the trigeminal ganglion is stimulated either in humans or the cat,[36] presumably by antidromic activation. Trigeminal neurons innervating the dura mater preferentially contain CGRP over substance P,[37,38] and this seems likely to be reflected in a preferential use of CGRP as a crucial

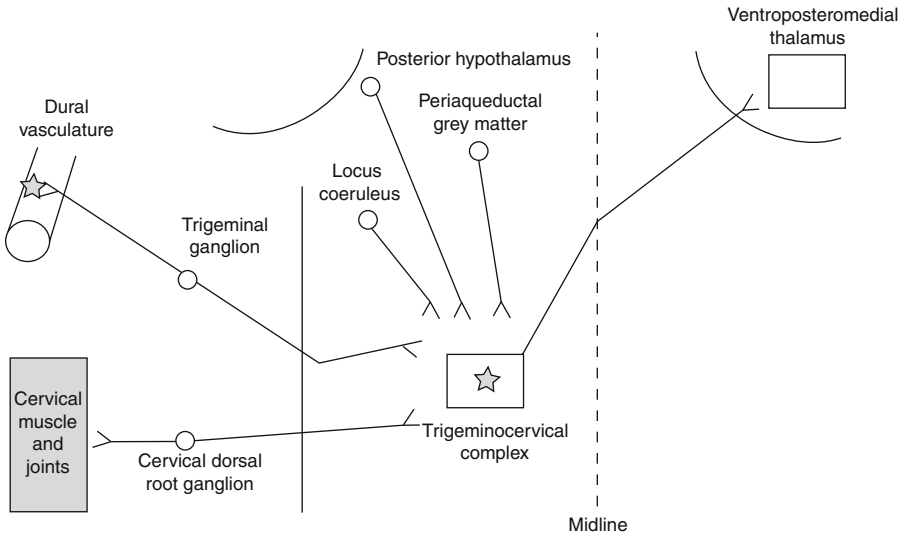

Fig. 1. Illustration of the trigeminovascular system, its projections and its modulatory inputs. Trigeminal neurons, whose cell bodies are found in the trigeminal ganglion, innervate pain-producing structures within the head that have calcitonin gene-related peptide (CGRP) receptors, and project to second-order neurons in the trigeminocervical complex. This complex receives input from cervical structures and projects to the contralateral ventroposteromedial thalamus. Trigeminocervical complex neurons are modulated by subcortical structures such as the locus coeruleus, periaqueductal grey matter and posterior hypothalamus. CGRP receptor antagonists could act at the sites marked by a star to inhibit CGRP actions peripherally or, probably more importantly, reduce nociceptive traffic through the trigeminocervical complex.

transmitter in the trigeminocervical complex (see section 2.3.2).

Stimulation of the cranial blood vessels, such as the superior sagittal sinus, is painful in humans[39,40] and, remarkably, faradic stimulation is more consistently painful than mechanical stimulation.[16] The human dural nerves that innervate the cranial blood vessels largely consist of small diameter myelinated and unmyelinated fibres[41-43] that almost certainly subserve a nociceptive function.

2.2 Physiology

Studies of human trigeminovascular physiology provide some insight into what may occur when this nerve system is activated. Injection of ethanol into the trigeminal ganglion leads to facial flushing[44] and increased facial temperature[45] ipsilateral to the injections. Moreover, facial flushing after thermocoagulation of the trigeminal ganglion for tic douloureux is limited to the distribution of the sensory division coagulated.[46] Onofrio[47] confirmed this observation and noted that divisions with previous damage sufficient to produce dense anaesthesia did not flush when coagulated. These observations were quantified by Drummond and colleagues,[48] who recorded increases of 0.5–2.0°C in facial temperature in the distribution of the division coagulated.

In experimental animals, stimulation of the trigeminal ganglion, or discrete branches of it, produces increases in skin temperature in the cutaneous distribution of the appropriate divisions of the trigeminal sensory nerve.[49] Cranial blood flow is increased after trigeminal ganglion stimulation in the cat,[30] monkey[50] and in humans.[51] In the cat, the vasodilatory response appears to be 80% mediated by the facial (greater superficial petrosal [GSP]) nerve dilator pathway and 20% mediated by antidromic activation of the trigeminal system.[30] The facial/GSP response is mediated through the sphenopalatine (pterygopalatine in humans) and otic ganglia[52] and employs vasoactive intestinal peptide as one of its transmitters.[53] The cerebral vasodilator effects of trigeminal activation are largely seen in

frontal and parietal cortices,[54] and are somatotopically specific.[55] The vasodilator effects of trigeminal nerve activation are unaffected by cortical spreading depression, which, in contrast, blocks hypercapnic vasodilation.[56] Trigeminal ganglionectomy reduces post-ischaemic cerebral vasodilation,[57] and the trigeminovascular innervation seems to be involved in seizure-induced changes in the blood flow of the brain.[58] Thus, the trigeminovascular system innervates the dura mater and pial blood vessels, and probably has a physiological role, broadly speaking, as a neural protector system. These observations in humans and animals suggest that any form of head pain may be accompanied by trigeminovascular activation and, to a large extent, it is the degree of activation and the somatotopic nature of the trigeminovascular system that underlies its involvement in migraine.

2.2.1 CGRP Alone Does Not Mediate Plasma Protein Extravasation

Stimulation of the trigeminal ganglion results in leakage of plasma proteins from the vascular space into the dura matter, a process termed neurogenic plasma protein extravasation (PPE).[59] Is this phenomenon relevant to migraine? First, considering CGRP, there is no direct evidence that CGRP alone will produce increased vascular permeability in the dura mater.[60] In a study in mice, CGRP was not active in the plasma extravasation assay[61] but was a potent vasodilator.[62] Consistent with this, and in contrast to mice who have a neurokinin-1 receptor knockout,[63] animals in which the α-*CGRP* gene is disrupted still have a plasma extravasation response to application of mustard oil to the ear, which in turn can be blocked by a neurokinin-1 receptor antagonist.[64] Maltos and colleagues[65] applied substance P or CGRP to exposed dental pulp, after first drilling into the tooth and then inserting a probe through the cavity onto the pulp. Given the pre-stimulus of the drilling, CGRP by virtue of vasodilation, but not acting alone, may have promoted Evans Blue leakage.

Secondly, PPE itself can be blocked by substance P and neurokinin-1 antagonists, such as vofopitant (GR 205171).[66] Several neurokinin-1 receptor antagonists have been studied for the prevention[67] and acute treatment[68-71] of migraine, and each one has failed to show an effect.[72] Moreover, the endothelin antagonist bosentan,[73] two specific PPE inhibitors, CP 122288[74,75] and GR 4991W93 (4991w93),[76,77] and the neurosteroid ganaxolone,[78] which are all effective PPE antagonists in animal experiments, have each subsequently failed to show an effect in studies of acute migraine treatment. Taken together, it seems unlikely that substance P-related mechanisms are important in migraine and equally doubtful that CGRP blockade alone would block neurogenic PPE. It seems unlikely that a mechanism related to PPE is pivotal in migraine, and it is certainly probable that the effects of CGRP receptor antagonists in migraine are unrelated to PPE.

2.3 Pharmacology

The trigeminovascular system, the cell bodies of which are found in the trigeminal ganglion, projects to the periphery to modulate the dural vasculature[79,80] and to the trigeminocervical complex to activate second order trigeminal neurons.[81] The importance of CGRP in influencing both the peripheral and central innervation of this system has been explored extensively in experimental animals.

2.3.1 The Peripheral Trigeminovascular Interface: Intravital Microscopy of Dural Blood Vessels and CGRP

Williamson et al.[79] demonstrated that electrical stimulation of the dura mater causes CGRP release from the pre-junctional nerve fibres innervating the dural blood vessels, resulting in reproducible vasodilation. Both CGRP- and electrically induced dilation of dural blood vessels can be blocked by the classic peptide CGRP receptor antagonist, $CGRP_{8–37}$.[79] Neurokinin-1 receptors are not important in mediating neurogenic dural vasodilation,[79] nor are adrenergic,[82] histaminergic[83] or cholinergic[84] mechanisms. However, there are important receptor systems that interact with CGRP in the dural neurogenic vasodilator response that suggest that CGRP receptor antagonists will provide effective therapy for those with migraine, and that

they will offer even further avenues for development of medications for this indication. These are briefly covered in the following sections.

CGRP, Triptans and Other Anti-Migraine Agents

It has been shown that the triptans block neurogenic vasodilation in the dura mater.[85,86] Flunarizine, a clearly effective preventive agent for migraine,[87] does not alter neurogenic vasodilation.[88] On the other hand, topiramate, which is also certainly effective as a preventive agent in migraine therapy,[89] does attenuate neurogenic vasodilation.[90] More work is required to understand the importance of CGRP-related mechanisms and preventive anti-migraine medications as a possible role for CGRP receptor antagonists in migraine prevention is considered.

CGRP and Nitric Oxide

Nitric oxide (NO) donors can induce migraine[91] and cluster headache.[92] NO donor-induced dural vasodilation can be antagonised by sumatriptan.[88] Dural vasodilation caused by CGRP infusion can be inhibited by inhibitors of endothelial NO synthase (NOS),[93] while neurogenic dural vasodilation can be inhibited by neural (n)NOS inhibitors.[93] These data, taken together with clinical data suggesting that NOS inhibition is useful in the treatment of migraine, further point to the likely utility of CGRP receptor antagonists in migraine[94] and to an important interaction between CGRP and NO in primary headache.

CGRP and Cannabinoids

Anandamide (AEA; arachidonylethanolamide) is believed to be the endogenous ligand to the cannabinoid CB_1 and CB_2 receptors.[95-98] Using the model of intravital microscopy, it has been shown that anandamide is able to attenuate both neurogenic dural vasodilation and CGRP- and NO-induced dural vessel dilation.[99] Anandamide is structurally related to capsaicin and olvanil (*N*-vanillyl-9-oleamide), and both are transient receptor potential (TRPV1) agonists,[100] having both an amide group and an aliphatic side chain. Using the intravital dural microscopy model, it has been shown that anandamide can dose-dependently dilate dural arteries by an action not blocked by the CB_1 receptor antagonist AM 251. However, the anandamide dural vasodilator effect was attenuated by the specific TRPV1 antagonist, capsazepine, and involved CGRP release,[101] just as the effect of capsaicin in the same model does.[102] Thus, the biology of anandamide receptors and their ability to influence the trigeminovascular system and interact with CGRP mechanisms offers an interesting area for further exploration.

CGRP and Transient Receptor Potential (TRPV1)

Bolus injections of capsaicin produce a reproducible dural vessel dilation that has been measured in the rat using intravital microscopy. The capsaicin-induced dilation can be inhibited by the TRPV1 antagonist capsazepine to a modest degree.[102] Capsaicin-induced dilation is also inhibited by the CGRP receptor antagonist, $CGRP_{8-37}$[102] and by trigeminal denervation.[103] While relatively few trigeminal ganglion cells produce TRPV1 receptors, perhaps about 16%,[104] and its dural vascular effects seem small in comparison to, for example, CGRP, its interaction with CGRP-related mechanisms deserves further exploration.

2.3.2 CGRP Receptor Antagonists Block Trigeminovascular Transmission

Olcegepant (BIBN 4096BS) is a potent, highly specific non-peptide CGRP receptor antagonist that is devoid of vasoconstrictive actions in humans.[105-107] Local microiontophoresis of olcegepant inhibits trigeminocervical neurons *in vivo*.[108] These data complement studies that demonstrate that triptans[109] and ergot alkaloids[110] can inhibit second-order trigeminal neurons when iontophoresed into the trigeminocervical complex. Moreover, electrophysiological or Fos protein studies using the model of superior sagittal sinus stimulation, which excites by consecutive depolarisation of trigeminal afferents,[111] or local dural stimulation,[112] show that aspirin (acetylsalicylic acid),[113] dihydroergotamine mesilate[114] and triptans[115-121] inhibit trigeminovascular transmission. Remarkably, GR 4991W93, which is a potent inhibitor of neurogenic PPE in the dura mater[76] but is ineffective in the treatment of acute migraine,[77] is also

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