INTRODUCTION

The trigeminal pain pathway, as related to migraine, is represented by three main sites: i) the trigeminal nerve and ganglion providing unmyelinated C fibers that innervate the vessels (the trigeminovascular system) and the central projections to the brainstem; ii) the trigeminal nucleus caudalis (TNC) in the brainstem; and iii) the brain as the site of pain consciousness. Each of these sites has been suggested to be the essential one in migraine pathophysiology. This review outlines the experimental findings that support the hypothesis that both peripheral and central components are involved in migraine pathophysiology and drug activity.

THE TRIGEMINOVASCULAR SYSTEM

Since the early '80s, the trigeminovascular system has been proposed (1) and studied (focusing on the activation of trigeminal fibres), in order to evaluate the peripheral component of the migraine attack and to identify the possible mechanisms of action of old and new migraine aborting drugs, namely ergot derivatives and triptans (2,3). The trigeminovascular system has
been challenged in the rat by both chemical stimulation (systemic capsaicin) and unilateral electrical trigeminal ganglion stimulation (UETGS) to induce oedema (vasodilation and plasma protein extravasation) in tissue receiving trigeminal innervation (dura mater, conjunctiva, eyelid, lip) upon release of vasoactive peptides from nerve endings (CGRP, SP) (2,3). This response is known as neurogenic inflammation (NI).

Degranulation of mast cells accompanies the oedema response in the same tissues (4) and a stimulation intensity-dependent increase of CGRP is observed during UETGS in the plasma obtained from the superior sagittal sinus (SSS) (5).

The antimigraine drugs dihydroergotamine (DHE) and sumatriptan (SUM), the first triptan to be synthetized and marketed for migraine attack treatment, were found to be effective in blocking the above responses (3,5-7). Thus, a peripheral, prejunctional mechanism of action was proposed for the drugs (8,9) – also in view of the fact that SUM, given at therapeutic doses, is not able to cross the blood brain barrier (BBB), unless the latter is altered (10). Interestingly, in the NI model, extravasation occurs in rat dura mater but not brain, which thus excludes the possibility that electrical stimulation of the trigeminal ganglion, although potent, could damage the BBB (2). An interesting finding is that UETGS, while inducing tissue oedema as explained above, also provokes conjunctival injection, tearing and rhinorrhoea on the stimulation side (personal observation), suggesting the presence of a trigeminal-autonomic reflex.

Increase of CGRP plasma levels is also reported in the cat following trigeminal ganglion stimulation, and in blood obtained from the jugular vein of humans during migraine attacks (11). The levels decrease in humans following SUM administration, and the pain improves as well. Although anecdotal, there are reports of NI in humans during headache. Gadolinium-enhanced MRI during migraine attacks is reported to be normal, thus ruling out damage to the BBB (12). While dural inflammation was not observed with this procedure, there is some evidence that NI, when measured by Tc99m-HAS SPECT scan (13), occurs in dura mater during the migraine attack, and retro-orbital oedema (vascular inflammation with plasma extravasation in the basal venous vessels of the skull) has been described using the same technique during the active period in cluster headache (14).

The relevance of peripheral trigeminal-autonomic activation is supported by the observation that a larger proportion of responders to SUM, rizatriptan and zolmitriptan is found among migraine patients in whom signs of neurovascular activation are present during attacks (15). Furthermore, orphan headaches such as SUNCT and hemicrania continua, which are characterised by severe pain and the presence of autonomic signs ipsilaterally to the pain, are now being considered for inclusion in a revised version of the IHS classification (16) together with other headaches with similar features, namely cluster headache and chronic paroxysmal hemicrania (17).

THE TRIGEMINAL PAIN PATHWAY AND CNS-PENETRATING 5-HT\textsubscript{1B/1D} AGONISTS

The NI model has been used for several years to predict the efficacy of other 5-HT\textsubscript{1B/1D} agonists. Second-generation triptans differ from SUM in their ability to cross the BBB at therapeutic doses. Some of those agonists, such as avitriptan, show little potency to block NI but are able to block migraine pain. On the contrary, the conformationally-restricted SUM analogue CP122,288 is a potent inhibitor of NI, but is not effective on migraine pain (18,19). It is possible that different receptor recruitment and mechanisms are involved and dose adjustment for the lack of clinical efficacy may be needed.

The central mechanism has been advocated since the migraine attack is regarded as a discharge from a central “generator”, probably locat-
ed in the brainstem (20). However, the central action of the “second-generation triptans” does not seem to have produced a greater efficacy on pain and headache recurrence. In fact, the degree of pain relief and pain freedom, as well as recurrence, is about the same for SUM and the newly synthetized triptans.

Activation of neurons, seen as increased c-fos expression in the TNC following trigeminal ganglion, dural or SSS stimulation in the cat, is blocked by local application of triptans with peripheral-central action (21,22). This activation represents an experimental secondary phenomenon to peripheral activity and it can be shut down not only by drugs with central action but also by drugs that block, primarily, peripheral components. CP122,288 (a potent inhibitor of NI but ineffective on migraine pain) does not block TNC cell activation, whereas eletriptan, which is able to inhibit both NI and c-fos expression in the TNC, is effective in blocking migraine pain (23). On the basis of these observations, the TNC is considered to be the possible site of action of CNS-penetrating compounds in migraine attack treatment. In vivo pretreatment with CP93, 129, SUM or DHE inhibits c-fos expression in the TNC induced by subarachnoid haemorrhage (24). c-fos activation following unilateral spreading depression is inhibited by both SUM and by trigeminal denervation, suggesting a role for peripheral fibres in this model and their involvement in the mechanism of action of the drugs (25).

A central action of SUM should be taken into consideration, given the reports of dystonia and of akathisia in migraine patients following SUM, and of the efficacy of SUM in treating palatal myoclonus (26-29). The presence of SUM binding sites is described in several CNS areas other than the TNC, and the substantia nigra also possesses SUM binding sites, providing a locus for drug activity in the above patients (30,31). SUM and zolmitriptan are able, when systemically administered or locally applied on brain slices, to abolish NOS and cGMP increase following NMDA receptor activation (32).

CONCLUDING REMARKS

Migraine is a complex pathology in which both central and peripheral components of the trigeminal pain pathway probably play a significant role, both in the symptoms and signs of the attack and in the mechanisms of action of antimigraine compounds. In fact, triptans, which constitute the most important therapy for aborting migraine pain, possess several mechanisms on serotonin receptor-mediated actions and some of them are still not completely understood. More detailed clinical research studies are needed in order to clarify what is still unknown about these drugs.

If the migraine generator is located in the brainstem, second-generation triptans should have been more effective than SUM in blocking migraine pain, due to their penetration of the CNS. However, the therapeutic gain obtained with these drugs is no higher than that obtained using SUM. And if passage of SUM through the BBB does effectively occur, this means that the new triptans do not represent a further tool in terms of either mechanism of action or efficacy. Drugs that are devoid of peripheral action should be designed in order to block the CNS generator at the beginning of an attack.

Patients with unilateral migraine pain show decreased pain perception threshold during corneal reflex recording (33). This observation suggests sensitisation of the peripheral and/or central pain pathway (34). From this perspective, the triptans can be regarded as inhibitors of the perpetuation of pain mediated by the peripheral component, i.e., the trigeminovascular system.

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