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Editorial

Sumatriptan : efficacy and contribution to migraine mechanisms

*"I think the sensory symptoms of the paroxysm are owing to a "discharging lesion" of the convolutions evolved out of the optic thalamus, i.e. of "sensory middle centres" analogous to the "motor middle centres". I believe the headache and vomiting to be post-paroxysmal." (J Hughlings Jackson)*¹

Recent therapeutic claims in migraine have been based on the responses of the intracranial circulation to manipulation of serotonin (5-HT) receptors. These prompt careful reappraisal, firstly, of what causes head pain, and more specifically, migraine; and secondly, of the claims of benefit for a new pharmacological agent.

Head pains arise from distension or inflammatory processes in sensitive intracranial structures : the dura, arteries and veins, paranasal sinuses, the eyes, and cervical spine. The innervation of all these structures is via the trigeminal nerve and the upper three cervical nerve roots.

On the afferent side there is the nucleus caudalis (a laminated part of the spinal trigeminal nerve to C1-C3.²³ Pain fibres descend in the spinal root of the trigeminal nerve to C2 where they converge with afferents from C1-C3 on second order neurons. This provides a pain pathway from head to neck and *vice-versa*.³ Efferent axons ascend to brainstem nuclei. The raphe nuclei and locus coeruleus project rostrally to the cortex, and caudally as part of the *endogenous pain control circuit*.² Stimulation of these brainstem nuclei and of the trigeminal complex increases extracranial blood flow by reflex connection with the parasympathetic part of the facial nerve - via the greater superficial petrosal nerve, sphenopalatine and optic ganglia. This constitutes a link between neural and vascular mechanisms, the "trigemino-vascular reflex".³

5-HT₁ agonists (for example ergotamine, sumatriptan) bind to vascular receptors and constrict dural and pial vessels. Plasma extravasation (PE) can be stimulated by perivascular sensory fibres which release neurokinin A, calcitonin G related peptide (CGRP) and substance P. These neuropeptides, present in unmyelinated C fibres, can be released by antidromic trigeminal stimulation from perivascular sensory axons; this induces vasodilatation and extravasation of plasma protein (neurogenic inflammation) with an increase in CGRP in the superior sagittal sinus.⁴ If pretreatment with dihydroergotamine and sumatriptan is given, the levels of CGRP in plasma are reduced, thus providing an explanation for blockade of neurogenic inflammation, the putative cause of pain.

Second order neurons can be suppressed by experiment-

al stimulation of the "endogenous pain control system" in the periaqueductal grey matter or, in a third of cases, by local application of ergot or the 5-HT₁ agonist sumatriptan. Changes in the cerebral and extracerebral circulations which simulate migraine with aura can be produced experimentally in the cat by stimulation of the locus coeruleus, dorsal raphe nuclei and parts of the trigeminal systems. Thus pain is modulated by interneurons regulated by a 5-HT pathway from the dorsal raphe nuclei and a noradrenergic path derived from locus coeruleus. We must be cautious of extrapolation to humans, since there is no valid animal model of migraine.

Monoamine depletion may open the gate control of pain and cause excessive transmission of impulses along second order neurons of the trigeminal and upper cervical pathways, inducing painful vasodilatation of meningeal vessels, thereby causing headache.

There is evidence of presynaptic (prejunctional) 5-HT receptors.³ 5-HT₁ receptors function as inhibitors and 5-HT₁ agonists relieve acute attacks; 5-HT₂ receptors are excitatory, and selective antagonists of 5-HT₂ (for example, methysergide) are of value in prophylaxis; 5-HT₃ receptors are also excitatory, relating to vomiting, but their role in migraine is not established. It is known that 5-HT₁ agonists fail to block PE in the dura mater following intravenous injection of neuropeptides; they block platelet accumulation, the development of endothelial vesicles, oedema formation in postcapillary venules, and mast cell degranulation; 5-HT₁ agonists attenuate increases in sagittal sinus CGRP levels during electrical stimulation.

Constriction of vascular smooth muscle (postjunctional action) is less likely, and the prejunctional action of 5-HT receptors on trigeminovascular axons mediates the effects of ergot and sumatriptan.⁵

Migraine attacks are not well understood, but depend on a primarily cerebral (neural) mechanism with a fluctuating threshold⁶ which determines the timing and pattern of attacks, the aura, and the consequent changes in pial microcirculation. This is linked to a vascular mechanism which accounts for the headache.^{4,5}

The release of pain producing vasogenic amines from blood vessel walls are accompanied by pulsatile distension which may account for vascular pain. This is evoked by neural triggers which may activate the trigeminovascular reflex² (vide supra). Burnstock's "purinergic" hypothesis⁷ suggests that adenosine 5'-triphosphate (ATP) and its breakdown products adenosine 5' monophosphate and

adenosine mediate the vasodilatation following the initial vasospasm. ATP stimulates primary afferent terminals in the cerebral vasculature. Studies have shown that the ATP induced cerebral vasodilatation depends on the endothelium being activated by P(2y)-purinoceptors on the endothelial cell surface and subsequently releasing endothelium-derived relaxing factor (EDRF). Endothelial cells are the main source of the ATP, although adenosine 5'-diphosphate and ATP released from clumped platelets may produce vasodilatation. A purinergic mechanism may also be involved in the initial local vasospasm, via P(2x)-purinoceptors on smooth muscle cells occupied by ATP released either as a cotransmitter with noradrenaline from perivascular sympathetic nerves or from damaged endothelial cells.

The aura is associated with regional spreading oligoemia (about 20% reduction of flow) which may be succeeded by increased extracranial blood flow during headache. In classic migraine, the slow march of neurological symptoms correlates with a wave of spreading oligoemia⁸ that traverses the cortex from the occipital region at 2–3 mm/minute. Cortical spreading depression is a slowly moving suppression of electrical activity that propagates across the cortex at a rate of 2–5 mm/minute, accompanied by a disruption of ion homeostasis, neuronal depolarisation and increased energy metabolism. The spreading oligoemia of classic migraine correlates with spreading depression evoked in animal experiments.⁹ Leão's theory¹⁰ that spreading depression plays a role in migraine pathophysiology has, however, not been reliably demonstrated in humans.¹⁶ As both Hughlings Jackson and Gowers noted,¹¹ cerebral vascular changes are *unlikely* to be fundamental to headache mechanisms and we now know that pain can start during cerebral oligoemia in classical migraine, and flow does not consistently alter during common migraine.¹² For comparison, in cluster headache, normal results are found for regional cerebral blood flow (rCBF) and SPECT [using hexamethylpropyleneamineoxime (TcHMPAO)] in small vessels during and between attacks. Transcranial Doppler studies show decreased velocity in the middle cerebral artery simultaneously with unaltered blood flow : suggesting vasodilatation.

The neural hypothesis of migraine, reiterates the writer's hypothalamic hypothesis¹³ of an internal clock reacting to a variety of diurnal circadian rhythms and to cyclical psychogenic, hormonal and vegetative activities. These in turn activate autonomic and brainstem pathways resulting in *secondary vascular changes* which release the inhibition of pain conveyed in the trigemino-vascular system : thence headaches. Painful distension of dural vessels, and of scalp arteries mediated through the greater superficial petrosal nerve explains the throbbing pulsatile pain in some subjects. Neuronal changes are primary, with secondary effects on the microcirculation causing oligoemia and the aura.

The cerebral mechanism is responsive to mood, emotions^{14 15} tiredness, stress, relaxation, hormonal changes, as well as to peripheral stimuli such as bright lights, noise and possibly atmospheric changes. Its threshold is susceptible to hypothalamic function which in turn is modulated by seasonal patterns, diurnal and biological clocks and by hormonal factors¹⁶—seen in the remission in pregnancy in many patients and a worsening in those on oral contraceptives.

Monoamine depletion of brainstem nuclei may result in low platelet serotonin storage or release. Reserpine precipitates migraine attacks and releases platelet and other stores of 5-HT.

The importance of 5-HT receptors is confirmed by the observations that intravenous 5-HT relieves headache;

reserpine (a 5-HT depletor) induces headache; and by the demonstrated efficacy of the 5-HT₂ antagonists, methysergide and pizotifen, as prophylactics,¹⁷ and of ergotamine and sumatriptan (both 5-HT₁ agonists) in treatment of acute attacks. But it is simplistic to regard migraine as a "low serotonin syndrome".

The fashionable neuro-excitatory chemicals, glutamate and aspartate (NMDA) have been investigated as putative initiators of "spreading depression" both between and during attacks. Higher blood levels were found between attacks in both migraine groups compared with tension headache and control subjects. Further elevations of glutamic acid were found during attacks.¹⁸ The results suggest a defective cellular reuptake mechanism for glutamate and aspartate in patients with, migraine which may indicate a similar defect in neurons and glia predisposing the brain of those with migraine to Leão's spreading depression.

Olesen has reconciled the vascular and neurogenic elements as a "vascular-supraspinal-myogenic model". Headache intensity is determined by the sum of nociception from cranial arteries and pericranial myofascial tissues which converge upon the same neurons and are under supraspinal facilitatory control. Vascular input dominates myofascial input in migraine,¹⁹ and *vice versa* in tension headache. Long term potentiation due to nociceptive activation and sensitisation of neurons may lower the threshold to headache.

The rationale for the use of drugs acting on 5-HT mechanisms depends on the presence of receptors for 5-HT in cranial arteries and elsewhere in the CNS, where they play a role in the neural control of cranial vessels and endogenous pain control systems (*vide supra*). Since migraine symptoms reflect both neural and vascular phenomena it is likely that 5-HT receptor activity is but one relevant factor. It is probable that many prophylactics act by central 5-HT₂ antagonism, whereas control of an attack relies on constriction of cranial vessels mediated by 5-HT₁ receptors.²⁰

Research on sumatriptan has helped to clarify 5-HT receptor functions and diversity, and has contributed to our still incomplete understanding of the pathogenesis of headache. Sumatriptan is a specific and selective agonist of 5-HT₁ receptors of cranial blood vessels causing vasoconstriction.²¹ It has negligible effects on 5-HT₂, 5-HT₃, dopaminergic, muscarinic or noradrenergic receptors (compared with ergotamine). Sumatriptan does not penetrate the blood-brain barrier and has no CNS effects. Systemically, it has no effect on pulse or blood pressure. It selectively reduces flow in the internal carotid arteries and in cranial and dural vessels. Intravenous sumatriptan does not change rCBF; it constricts the carotid vascular bed, but has no effect on pial vessels in cats. It has 96% bioavailability subcutaneously and 14% orally, with a plasma half-life of 2 hours. Its clearance is 80% by the liver, 20% by the kidneys where it is excreted as an indole acetic acid analogue.

Early trials of the subcutaneous preparation in a 6 mg dose²² showed relief of headache in 77% patients at 60 minutes, and in 83% at 2 hours with corresponding improvement in nausea, vomiting and photophobia. It is also effective in cluster headache with relief of symptoms at 15 minutes in 74% compared with 26% given placebo.²³

The subcutaneous preparation will almost certainly be superseded by oral medication (100 mg) which provides relief in about 70% of attacks within two hours. Second and third attacks respond as well as the first. Comparative trials have shown slight, but significant superiority to aspirin 900 mg plus metoclopramide 10mg. Legg *et al* (1990 unpublished information) reported 358 pts in 3

consecutive attacks of migraine. In the first attack, 56% responded to sumatriptan; 45% responded to aspirin and metoclopramide ($p = 0.078$). In the second and third attacks the responses were 58 and 65% for sumatriptan, 36 and 34% for aspirin and metoclopramide ($p = 0.001$).

The onset of relief is faster but there is a higher rate of minor side effects. Recurrence of headache within 48 hours was 42% for sumatriptan and 33% for aspirin and metoclopramide.²⁴ In a randomised double-blind comparison of sumatriptan and cafergot,²⁵ 100mg oral sumatriptan relieved headache after 2 hours in 66% compared with 48% of those given oral cafergot. However, the well known poor oral absorption of ergotamine is a serious limitation of this study and comparison with inhaled or rectal ergotamine will be of importance.

Goadsby *et al*²⁶ recently showed a good response to oral sumatriptan in 51% of patients at 2 hours compared with 9% given placebo; rescue medication was needed in 41% of the sumatriptan group, but in 88% of the placebo group. Of 28 patients who were free of headache at 2 hours, 11 (39%) had recurrent headache within 24 hours, a significant rebound effect which may owe as much to the natural history of migraine as to a true pharmacological effect.

Toxicity was not a major problem in 6500 patients and 35 000 attacks.²⁷ There are so far, no proven cardiovascular, CNS or other serious sequelae. Vague chest discomfort occurs in one third of patients and is a cause for some concern as a transient 13% reduction of coronary lumen has been shown; but ECG changes are rare and coronary angiography has shown no instance of occlusion. Nausea, vomiting, taste disturbance, tingling, all deemed mild and transient, occur in about 38% patients within the first 4 hours. The problem of recurrence (? rebound) in about one third of patients needs to be clarified by experience, especially since a second headache responds well to further sumatriptan, but obviously compounds the pressing issue of cost.

Sumatriptan appears to be a significant advance in migraine treatment.²⁸ It is an effective, safe and prompt remedy for the acute attack, suppressing all the symptoms, not just headache alone. However, it works in 70% of sufferers—not in every patient. The present high cost (£41 for two injections, £8 for one 100 mg tablet) limits its use.

In an attack, aspirin, paracetamol or codeine, combined with anti-emetics form the first line of treatment. Ergotamine (usually by suppository or inhalation) remains effective in 50–60% and is useful if too frequent doses are avoided. However, for patients prone to unusually refractory, severe or inconveniently timed attacks, sumatriptan promises to be the drug of choice. Before its final place in

migraine treatment can be defined wider clinical experience is needed.

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