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Current Opinion in Pharmacology

Understanding the pharmacology of headache

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Migraine continues to be the most common of the debilitating headaches. Existing acute headache treatments are not always satisfactory, and current research is focussed on targeting neuroinflammatory pathways with drugs that are devoid of vascular action. Current prophylactic drugs are largely centred around antihypertensive, anticonvulsant and antidepressant drugs, although not all drugs of all sub-classes in these categories are effective. Selective agents which target the neuroinflammatory process including targets such as calcitonin gene related peptide, and PANNEXIN 1 may have clinical utility.

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Current Opinion in Pharmacology 2014, **14**:30–33

This review comes from a themed issue on **Neurosciences**

Edited by **David G Trist** and **Alan Bye**

For a complete overview see the Issue and the Editorial

Available online 22nd November 2013

1471-4892/$ – see front matter, Published by Elsevier Ltd.

http://dx.doi.org/10.1016/j.coph.2013.10.005

Introduction

Headache is one of the commonest symptoms in the community. Although there are many effective treatments, the relatively small proportion of patients who do not have a satisfactory outcome with current treatments still represents a large number of people with unsatisfactory outcomes. Given that headache patients are generally younger people of working age, this additionally represents a large economic burden to society and hence there is an important unmet medical need to address [1]. However, for several reasons, developing new treatments for headache on a pharmacologically rational basis is difficult.

The first problem is that for the main types of headache we still do not have good mechanistic understanding of the condition. For migraine, by far the most studied condition, there is reasonable consensus that this is a disorder of neuronal excitability causing paroxysmal spreading depression which leads to a sterile inflammatory response with pain [2•]. Very recently one part of the missing link describing how aura could cause the inflammatory response has been established by activation of pannexin-1 channels and this may represent a new therapeutic target [3••]. However, for the more common condition of tension-type headache, apart from a general consensus that this somehow represents a state of acquired central sensitisation with some peripheral involvement, the pathways by which this occurs are unclear [4]. The much rarer but clinically dramatic presentation of cluster headache can bring extreme suffering to the patient, such that an American survey showed that more than half the patients have considered suicide to exit the condition [5]. Despite the strikingly unusual phenotype, there has been little research into the mechanisms involved in cluster headache and most treatments have been found opportunistically.

Pathophysiology of headache

Much of the lack of understanding the mechanisms of headache is due to the absence of suitable animal models. Various animal models have been proposed for migraine including neurovascular [6] and inflammatory [7] models, but these do not replicate most of the aspects of the condition. For migraine, the development of new treatments has been fairly rational. The first mechanistically plausible hypothesis for migraine was that of Wolff who hypothesised that migraine was due to cerebral vasoconstriction causing aura, and cerebral vasodilation causing pain [8]. It is now recognised that low cerebral blood flow is a consequence rather than a cause of aura [9] and intracranial and extracranial blood vessels are not dilated in migraine [10••]. However, the initial Wolff hypothesis was plausible and the hunt for selective cerebral vasoconstrictors initially led to the ergots. These drugs have complex pharmacology, interacting at a wide range of receptors but undoubtedly have some vasoconstrictor properties [11]. Indeed the main clinical problem with this class of drugs when used too frequently is peripheral vasoconstriction and tissue ischaemia [11]. The multiple receptor activities are also a mixed blessing. For example, methysergide is probably an effective migraine prophylactic drug although its agonist activity at 5HT2B receptors is probably responsible for the occasional serious but irreversible complications of cardiac valve and retroperitoneal fibrosis [12].

Acute treatments

The story of the discovery of the triptans has been well documented by the discoverer of sumatriptan, Pat Humphrey [13]. It had been noted in the 1960s that intravenous serotonin appeared to be effective in migraine, but was unsuitable as a treatment due to widespread adverse

effects in the vascular and pulmonary systems. However, it was hypothesised that a selective cerebral vasoconstrictor mimicking some but not all of the effects of 5-HT would be effective. In early clinical development, sumatriptan was noted to cause chest pain reminiscent of angina and given its putative vasoconstrictor properties this was of concern. It is now clear that this is a class effect and only very rarely ever associated with true cardiac ischaemia and hence the nature of this class of symptoms is still unknown. Given that sumatriptan is relatively polar, early studies confirmed that little drug entered the brain [14]; the striking clinical efficacy of injected sumatriptan was taken as confirmation of the vascular hypothesis of migraine and that a selective cerebral vasoconstrictor was a rational treatment. However, subsequent research demonstrated that triptans are not selective cerebral vasoconstrictors but cause a modest reduction of around 15% in conductance vessels throughout the body, and is not selective for the cerebral vasculature [15]. Additionally, a number of unequivocally central phenomena have been ascribed to sumatriptan (and other triptans) and in clinical practice the drug is accompanied by CNS-type adverse effects such as lethargy as reflected in the product information. It is now accepted that at least some of the effects of sumatriptan and other triptans are due to modulation of the ascending central pathways from the trigeminal tract [16]. Although there have been attempts to make triptans with superior pharmacokinetic or pharmacodynamic properties, this is not translated to any one drug being clearly the best in class although individual patients may favour one or the other [17]. Agonists targeted at other non-vasoconstrictor 5HT receptors, $5HT_{1F}$ and $5HT_7$, show promise [18••].

Another class of anti-migraine therapies with rational basis is the small molecule receptor antagonist calcitonin gene-related peptide (CGRP) [19]. CGRP was known to reside in peripheral nerve terminals in the vasculature and confirmation of their role in migraine was confirmed by Goadsby *et al.* who showed an increase in plasma concentration of CGRP in the internal jugular vein in a patient in the ipsilateral headache side in patients suffering from migraine, and that normalisation of such levels occurred following successful attenuation of the treatment with sumatriptan [20]. Several orally bioavailable small molecule receptor antagonists of CGRP have been in development, but their route to market has been hampered by hepatic toxicity and it is unclear whether any of these will reach commercial success [18••,21•]. An interesting alternative approach is the use of monoclonal antibodies against the CGRP receptor [21•,22]. The potential attractiveness of this approach is a 'vaccination' approach in which patients could receive a single injection which may provide prophylaxis for a month or more. However, such antibodies will clearly not cross the blood–brain barrier and we await the results of phase II studies to see whether such compounds are effective.

In addition to the migraine-specific treatments mentioned above, non-specific analgesics and antiemetics are still the best choice for some patients. Paracetamol, aspirin, other non-steroidal anti-inflammatory drugs are effective [23]. There is a general consensus that opioids and combination products containing opioids, including codeine, are best avoided except for very infrequent use when other acute treatments have failed [24]. Most classes of acute headache therapy have been associated with an increasing frequency of headache, which reduces once the medication is withdrawn, a condition known as medication overuse headache (MOH) [25]. However the class of drugs which has by this far the strongest association with medication overuse headache is the opioid class [26•]. We have hypothesised that this is due to paradoxical glial activation causing a chronic neuroinflammatory state [26•].

Prophylactic drugs

A wide range of drugs has been shown to be efficacious in reducing the frequency of migraine. Generally such drugs reduce the frequency but do not significantly change the attack phenotype although this can occur. There is no currently accepted unifying mechanism by which such drugs work. The majority of migraine prophylactic drugs come from cardiovascular or antidepressant and anticonvulsant classes. Indeed the success of some of the early cardiovascular drugs such as propranolol was taken as confirmation of the vascular hypothesis of migraine. The efficacy of propranolol does appear to be due to its beta blocking action, not from off target effects, as all beta blockers without intrinsic sympathomimetic activity appeared to be effective [27]. Other antihypertensive drugs which are shown efficacy in migraine include candesartan [28] and lisinopril [28]; how the mechanism of action of these drugs are not clear and it is also uncertain whether other drugs of these therapeutic classes are effective.

Although all tricyclic antidepressants appear to have some efficacy in migraine [29], this appears to be independent of the antidepressant action and patients did not need to be depressed for them to work. However the selective serotonin reuptake inhibitors appear not to be generally effective in migraine [30] and in a significant number of patients make them worse. The role of the SNRIs is unclear [31]. Tricyclics are the treatment of first choice in tension-type headache, where in fact very few treatments have been shown to be effective [29].

Several anticonvulsants such as valproate [32] and topiramate [33] have been shown in multiple studies to be effective in migraine. These two drugs are approved by regulatory authorities for use in migraine. However this