EDITORIAL

Headache

INTRODUCTION

Migraine is a highly disabling,[1] common,[2] and expensive[3] brain disorder.[4] The development of triptans, serotonin 5-$HT_{1B/1D}$ receptor agonists,[5] was a substantial advance in acute migraine therapy, although only one third of patients are headache-free 2 hours after treatment.[6] Moreover, there are important contraindications to their use in the setting of cardiovascular and cerebrovascular disease.[7] Against this background, both new formulations of current medicines and altogether new approaches to treatment are being developed. The articles in this issue of *Neurotherapeutics* address a common theme: better treatment of patients with headache disorders. The goal here was to review a range of investigational approaches highlighting new delivery methods, new pharmacological targets, and novel nonpharmacological targets. The issue was designed to give pause for thought to clinicians and developers of medicine, and hope for patients whose current treatments are inadequate.

IMPROVING CURRENT TREATMENTS

An important issue in the treatment of migraine is the gastrointestinal disturbance that causes discomfort in the form of nausea or vomiting, or both,[8] and may limit the absorption of medications.[9] This has been well recognized for some years on a worldwide basis, with probably the most widely used solution in the past being the ergotamine/caffeine suppository. This formulation is at least as effective as sumatriptan suppositories.[10,11] In this issue, Silberstein (page 153) broadly addresses the development of new formulations of sumatriptan, dihydroergotamine, and diclofenac, each aimed at better or more rapid absorption, with or without improvements in tolerability. The sumatriptan transdermal patch, reviewed in this issue in detail by Pierce (page 159), is described as a medicine delivery using an iontophoretic approach that completely bypasses gastrointestinal issues in migraine and may provide some advantages in terms of reduced side effect burden.[12] For patients who are needle-averse, a needle-free device,[13] with excellent absorption characteristics, is covered by Silberstein in this issue. Similarly, a novel inhaler system is described that delivers a well-characterized medicine, dihydroergotamine, by a nonoral route. With rapid onset, good pain-free rates, and the suggestion of effects lasting out to 48 hours,[14] this seems an important development.

SMALL MOLECULE THERAPEUTIC MEDICINE DEVELOPMENTS

Serotonin $5HT_{1F}$ receptor agonists

Although many patients will require an alternative to the oral route, taking a tablet clearly remains the most favored approach. To this end, new targets have been identified for which orally active drugs are being developed.[15] One promising approach covered by Reuter in this issue (page 176) is the development of serotonin 5-HT_{1F} receptor agonists. A number of the triptans, including sumatriptan, eletriptan, naratriptan, and zolmitriptan, are active at the $5HT_{1F}$ site, in addition to their well-recognized actions on $5HT_{1B/1D}$ receptors.[16] An action on $5HT_{1F}$ receptors is not required for the triptan antimigraine effect, because alniditan a $5HT_{1B/1D}$ receptor agonist without $5HT_{1F}$ effects,[17] is as effective as sumatriptan in the acute treatment of migraine.[18] However, it has been shown with the specific $5HT_{1F}$ receptor agonist LY344869 that the inhibition of trigeminocervical neurons with nociceptive trigeminovascular inputs has an independent $5HT_{1F}$ component.[19] Moreover, an earlier $5HT_{1F}$ receptor agonist LY334370[20] was shown to be effective in migraine. Consequently, it may be possible to treat migraine with highly $5HT_{1F}$ selective agents. The new data for COL-144, a nonvasconstrictor $5HT_{1F}$ receptor agonist, are covered by Reuter and represent an important advance.

Nitric oxide synthase

In this issue, Olesen (page 183) discusses the role of nitric oxide synthesis (NOS) and its inhibition in migraine. His group was the first to suggest a potential role for NOS inhibition as a treatment approach, based on a study of L-N^G-monomethyl arginine, a non-specific NOS inhibitor in migraine.[21] Olesen's work has also suggested a role for NOS inhibition in the treatment of chronic tension-type headache.[22] The NO donors clearly trigger headache,[23] and so the aim of development candidates is inhibition of nonvascular NOS. It seems likely that inducible NOS (iNOS) is not an important target, because randomized controlled trials of selective iNOS inhibitors in both prevention[24] and acute therapy[25] have failed. Enthusiasm for specific neural NOS (nNOS) inhibition has been dampened by the finding that a novel molecule

with both nNOS and $5HT_{1B}$ receptor agonist effects was not clinically successful.[26]

Neuropeptide targets in migraine

Calcitonin gene-related peptide. Of the current nonserotonin strategies to migraine therapy, approaches involving calcitonin gene-related peptide (CGRP) receptor antagonism seem most promising. The CGRP is elevated in acute migraine,[27] and its levels normalized by sumatriptan.[28] These observations led to the development of specific CGRP receptor antagonists,[28] such as olcegepant (BIBN4096BS)[29] and telcagepant.[30,31] Intravenous olcegepant is effective in acute migraine,[32] as is oral telcagepant.[33] The CGRP receptor antagonists have no vasoconstrictor action and represent a substantial advance in therapy that is clearly described, along with potential mechanisms of action by Edvinsson in this issue (page 164), who has worked on and indeed evoked the very concepts around this new approach.

Pituitary adenyate cyclase activating peptide. Human experimental studies described by Schytz et al. in this issue (page 191) implicate the pituitary adenyate cyclase activating peptide (PACAP) receptor in migraine. The PACAP levels are raised with nociceptive trigeminovascular stimulation.[34] The PACAP38 induces migraine and vasodilation,[35] whereas vasoactive intestinal polypeptide induces vasodilation, but not migraine.[36] The data implicate the PAC1 receptor and offer a further interesting target for therapeutics development.

Nerve block and device-based strategies

Even in the most experienced hands, some patients with migraine do not respond to or do not tolerate the medicines that are available. How one should define "medically-refractory" is a much-debated issue[37] whose mechanism is unknown.[38] However, the idea that such patients exist seems beyond doubt.[39,40] For such patients nonpharmaceutical treatments are being developed.

In this issue, Levin (page 197) discusses the place of nerve blocks. Various cranial and cervical targets have been suggested, although controlled trial data is limited. This area needs greater study because it is widely used, it is considered to be useful by experts, and yet clearly it is without a sufficient, objective evidence-base to be certain of the usefulness of these therapies.

Occipital nerve stimulation. In this issue, Paemeleire and Bartsch (page 213) discuss occipital nerve stimulation (ONS). There have been two studies of ONS in migraine: ONSTIM[41] and PRISM.[42] Both failed their primary endpoints. The ONS does appear on objective grounds to alter thalamic transmission in a way that would be logical in migraine.[43] This can be understood, in part, on the basis of interactions between second order trigeminal and cervical afferents.[44,45] In addition, there could be higher-order processing implications. Studies in cluster headache[46] and hemicrania continua[47] suggest that this therapeutic approach may have generic use in primary headache disorders. More work is clearly required.

Deep brain stimulation. A decade ago it would have been almost inconceivable to be writing on the subject of deep brain stimulation, yet the combination of novel neuroimaging work[48,49] and exciting translational surgery work[50] has made this an option. In this issue, Leone et al. (page 220) review the latest position for deep brain stimulation in cluster headache and the other trigeminal autonomic cephalalgias. It is very promising to have a new therapy for these patients whose lives are devastated when medicines fail them.

Transcranial magnetic stimulation. Lipton et al.[51] reviews recent work with the novel approach of transcranial magnetic stimulation in migraine (page 204). Data from the first randomized controlled trial suggests that single pulse transcranial magnetic stimulation can be used to treat migraine when patients with aura are selected. The approach seems safe and well tolerated. It is based on the concept that migraine aura is similar to the animal phenomenon of cortical spreading depression.[52] Moreover, experimental work suggests that indeed transcranial magnetic stimulation can alter cortical spreading depression in experimental animals.[53] A simple, safe, and effective therapy without side effects would certainly be welcomed by many migraineurs.

Disclosure

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