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Perspectives in the Therapeutic Treatment of Migraine

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ABSTRACT

Migraine is a disabling disease which affects around 10% of the global population. It is characterized by a strong unilateral and pulsatile headache which is sometimes accompanied by nausea, vomiting, photophobia, phonophobia and other neurological symptoms. During migraine, alterations in the metabolism of serotonin (5-hydroxytryptamine; 5-HT) and in the dynamics of calcitonin gene-related peptide (CGRP) result in vasodilatation of meningeal blood vessels and in facilitation of trigeminal pain integration. The above conditions play a role in the painful phase of migraine. Regarding therapeutic alternatives, classical antimigraine drugs, such as the ergots (e.g. ergotamine and dihydroergotamine), produce cranial vasoconstriction, inhibit trigeminal vasodilatation and inhibit trigeminal pain integration, but some undesirable hypertensive mechanisms induced by systemic vasoconstriction are favoured. These problems led to the development of more selective antimigraine agents like the triptans (serotonin 5 HT1B/1D/1F receptor agonists), which represent the current mainstay of acute antimigraine treatment. However, the triptans: (i) may produce vasoconstriction of coronary blood vessels; (ii) are effective in less than 50% of migraine patients; (iii) are clearly contraindicated in patients with cerebro- and cardiovascular disease; and (iv) do not seem to be useful as prophylactic agents.

Hence, more recent antimigraine alternatives include the development of CGRP receptor antagonists (e.g. olcegepant, telcagepant) and human monoclonal antibodies towards CGRP and the CGRP receptor. These antibodies are currently in clinical trials for the treatment of both episodic and chronic migraine with promising results. In short, the inhibition of the CGRPergic system (devoid of triptans-related vasoconstriction) is therapeutically similar to the antimigraine efficacy of the triptans, but hypothetically with fewer side effects. However, chronic blockade of CGRP receptors may represent a potential cardiovascular risk. Meanwhile, the triptans are currently considered the best therapeutic option to abort migraine attacks. The lack of a preventive drug is a persistent necessity for migraine therapeutics.

INTRODUCTION

Migraine is a highly disabling disease characterized by a strong and pulsatile unilateral headache which affects 10% of the world population according with the world health organization [1]. The “Headache Classification Committee of the International Headache Society” [2] describes several and complex neurological signs and symptoms which may occur before and during migraine. Before migraine attacks, premonitory symptoms such as yawning and scintillating scotoma (aura) may occur [3]. Migraine attacks are sometimes accompanied by allodynia, hyperalgesia, photophobia, phonophobia, anorexia, nausea, vomiting, etc. Pain during migraine is restricted to the head, which suggests the main role of the trigeminal system [4]. All these features dramatically affect the quality of life, not only of the patients, but also of their close family members as well as their social and professional activities.

One interesting aspect of migraine is its higher prevalence in female patients; the ratio is almost 3:1 during the adult life [5]. The origin of this difference seems to be related with hormonal changes in view that the prevalence of migraine: (i) is quite similar in girls and boys under age 10; and (ii) decreases after menopause [6]. On the other hand, there is a correlation between migraine and several psychiatric disorders (e.g., depression) which increase the risk to develop migraine from acute attacks to a chronic problem and consequently to increase the risk for impairing the psychiatric condition [7-9]. A patient with chronic migraine may develop more than 15 attacks per month, which may represent the potential loss of school, job and/or spouse. For all these reasons, the correct treatment of migraine is determinant to protect the quality of life of migraine patients. Fortunately, our knowledge about the pathophysiology of migraine has increased substantially in the last decades [10,11]. However, there is not a specific drug created to migraine prophylaxis in the market.

Pathophysiology of Migraine

The pathophysiology of migraine is highly complex and involves alterations in several areas in the brain (e.g., the cortex, the trigeminal nucleus, the hypothalamus, etc.) and in the periphery (the vasculature, the ophthalmic branch of the trigeminal ganglion, the meninges, etc.) [3]. Among these alterations, an increase in the release of neuropeptides from sensory perivascular nerve terminals, particularly calcitonin gene-related peptide (CGRP) and impairment in the metabolism of serotonin (5-hydroxytryptamine; 5-HT) seem to be involved in the pathophysiology of migraine [12,13].

For many decades, the origin of pain during migraine attacks was discussed considering a vascular vs. neural origin [14]. This discussion probably arose from some similarities between the systems of cellular control involved in modulating the meningeal vascular tone and the trigeminal pain integration. Nevertheless, migraine is currently considered a neurovascular disorder, and both the serotoninergic and CGRPergic systems are highly related with vascular modulation and pain integration [13,15,16]. Interestingly, the decrease in 5-HT levels and the increase in CGRP result in similar events, namely: (i) vasodilatation; and (ii) pain integration. In addition, acute antimigraine therapy with triptans (e.g. sumatriptan, zolmitriptan, eletriptan, which are selective serotonin 5 HT1B/1D/1F receptor agonists) or gepants (e.g. olcegepant or telcagepant, which are selective CGRP receptor antagonists) results in: (i) prevention of vasodilatation and (ii) analgesia [15-17]. Although the origin of pain in migraine is not completely clear, both neuronal and vascular alterations must be important during the painful phase [18, 19]. Accordingly, the classical therapeutic tools to treat migraine have been developed in an attempt to prevent/revert the vascular dilatation as well as the trigeminal pain integration.

Therapeutic Treatment of Migraine and Future Perspectives

After the ergots (ergotamine, dihidroergotamine), which are probably the first occidental anti-migraine drugs (still in therapeutic use), the triptans (e.g. sumatriptan, zolmitriptan, eletriptan, which are selective serotonin 5 HT1B/1D/1F receptor agonists) were developed in order to avoid vasodilatation of the blood vessels which irrigate the meninges [17]. These agents currently represent the first selective therapeutic option to abort migraine attacks [20]. The triptans induce two main effects: (i) selective vasoconstriction of the extracranial branches of the external carotid vascular bed which, in turn, hypothetically reduce the permanent activation of mechanoreceptors expressed on sensory nerves which sense the dilatation of the blood vessels irrigating the meninges and (ii) central and peripheral inhibition of mechanisms involved in pain integration [17,21]. Notably, the effects of triptans are quite similar to those from the ergots, but with less side effects [22,23]. In spite of this, the triptans still represent the potential for cardiovascular risks in chronic use or in patients with cardiovascular pathologies in view that these agents may produce vasoconstriction of coronary blood vessels. In addition, the triptans: (i) are effective in less than 50% of migraine patients; (ii) are clearly contraindicated in patients with cerebro- and cardiovascular disease; and (iii) do not seem to be useful as prophylactic agents.

The above problems related with the cardiovascular risk potential of the triptans led to the development of the gepants (e.g. olcegepant and telcagepant), which are potent non-peptide CGRP receptor antagonists with acute antimigraine properties [11,24,25]. However, the therapeutic use of the gepants had to be discontinued because of the risk of hepatotoxicity and formulation issues [11,26].

An alternative approach has recently led to the development of human monoclonal antibodies towards CGRP and the CGRP receptor. These antibodies are currently in clinical trials for the treatment of both episodic and chronic migraine with promising results [26,27]. Despite this progress, it must be highlighted that CGRP plays an important role in the modulation of many physiological functions and, hence, the potential side effects associated with abolishing (acutely or chronically) the actions of CGRP or its receptors remain largely unknown [12]. Within this context, it is noteworthy: (i) the existence of circulating picogram levels of CGRP in basal conditions; (ii) the capability of CGRP to inhibit the release of noradrenalin, ATP and neuropeptide Y from sympathetic nerves; and (iii) that CGRP knockout mice (as compared to wild type mice) have significantly higher values of mean blood pressure as well as noradrenaline in plasma and urine [12,28,29]. Accordingly, further basic and clinical research studies must investigate the potential cardiovascular risks associated with abolishing (acutely or chronically) the actions of CGRP or its receptors by using antagonists or antibodies for CGRP.

Admittedly, there are other non-classical therapeutic approaches in clinical trials (not discussed here), which are directed towards aborting and preventing migraine attacks. These include, amongst others, Botox, cannabinoids and topiramate[30-32]. All these alternatives are effective in some migraineurs and suggest that the development of a multi-target therapy may be another plausible choice; however, side effects are always an important issue in this kind of therapy.

Following this line of reasoning, Novel perspectives of the pathophysiology of migraine have explored alterations in the neurohormonal and metabolic integrity. For example, Dzugan&Dzugan [33] reported that the restoration of this integrity seems to be enough to abolish the attacks of migraine. If confirmed, this result represents an important contribution to the therapeutic treatment of migraine and opens the door to new alternatives with minimal side effects.

In conclusion, it is expected that the progress in understanding the pathophysiology of migraine may lead to the incorporation of novel therapeutic drugs directed towards aborting or preventing the attacks with minimal side effects. Among these novel therapeutic approaches: (i) the interference with CGRPergicpathways seems to be promising, but the evaluation of the hypertensive potential must be carefully considered; and (ii) the alternative of restoring the neurohormonal and metabolic integrity of migraine patients should be also comprehensively evaluated.

CONFLICTS OF INTEREST

The authors state no conflict of interest.

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