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Review

Challenges in developing drugs for primary headaches

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ABSTRACT

This review considers the history of drug development in primary headaches and discusses challenges to the discovery of innovative headache therapeutics. Advances in headache genetics have yet to translate to new classes of therapeutics and there are currently no clear predictive human biomarkers for any of the primary headaches that can guide preventative drug discovery and development. Primary headache disorder subtypes despite common phenotypic presentation are undoubtedly heterogeneous in their pathophysiology as judged by the variability of response to headache medicines. Sub-classification of headache subtypes into more homogenous and specific phenotypes groups may facilitate genotyping and provide sentinel patient groups that can be used in a mechanism specific manner to test new and more personalized treatment strategies in headache medicine. The development of the triptan class of serotonin 5-HT1B/1D/1F receptor agonists has advanced our understanding of the neurobiology of migraine pain, which subsequently resulted in the development of calcitonin gene-related peptide (CGRP) modulators that are now showing promise as acute and preventative anti-migraine agents. Despite these successes, there have been many near misses and failures in the discovery and development of headache therapeutics. Glutamate receptor antagonism whilst efficacious has central side effects and some approaches such as nitric oxide synthase inhibition, substance P antagonism and cortical spreading depression blockade, despite having promising effects in basic pain models, have not delivered efficacy in the clinic. Future efforts may triage novel physiological mediators using human experimental models of headache pain to support drug discovery strategies that target active pathways pharmacologically.

Contents

Abbreviations: CGRP, calcitonin gene related peptide; CSD, cortical spreading depression; NSAIDs, non-steroidal anti-inflammatory drugs; 5-HT, 5-hydroxytryptamine; 5-HIAA, 5-hydroxyindoleacetic acid; NO, nitric oxide (NO); TG, trigeminal ganglion; TNC, trigeminal nucleus caudalis; SP, substance P; BBB, blood brain barrier; iGLuRs, ionotropic glutamate receptors; mGLuRs, metabotropic glutamate receptors; NMDA, N-methyl D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; cAMP, cyclic adenosine monophosphate; mABs, monoclonal antibodies; eNOS, endothelial NO synthase; iNOS, inducible NO synthase; LNMMA, L-NG methylarginine hydrochloride; GTN, glyceryl trinitrate; NXN-188, NXN-188 dihydrochloride; NK, neurokin receptor; PACAP, pituitary adenylate cyclase activating polypeptide; VIP, vasoactive intestinal peptide; TTH, tension-type headache; CTTH, chronic tension-type headache; AMT, amitriptyline; TACs, trigeminal autonomic cephalalgias; CH, cluster headache; PH, paroxysmal hemicranias; HC, hemicrania continua; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection, tearing and rhinorrhea; SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; SSN, superior salivatory nucleus; GON, greater occipital nerve; ONS, occipital nerve stimulation; SPG, sphenopalatine ganglion; EFNS, European Federation of Neurological Societies.

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1. Introduction

The pathophysiology of headache is diverse with as many as 50 primary headache subtypes and 200 secondary headache subtypes (International Classification Committee of the International Headache Society (IHS), 2013). It has been estimated that 3% of the world's adult population suffer chronic headache on 15 or more days every month (Stovner et al., 2007). Migraine alone affects 15% of the world's population (Vos et al., 2012), and has been shown to be the seventh-highest specific cause of disability worldwide (Vos et al., 2012). Over the past 20 years headache drug development has yielded few innovative headache treatments and there remains a significant unmet medical need worldwide. Headache is largely treated with generic or reformulated drugs today, but inconsistent efficacy and side effects of many of the major drug classes leave ample opportunities for new headache therapies.

Advances in pain and headache genetics and better understanding of the neurobiology of headache have yet to translate to new classes of therapeutics. One primary challenge in headache science is that the pathophysiological basis of primary headaches is, despite great advances in the neurobiology of pain, still not clearly elucidated. Moreover, primary headache diagnoses, with few exceptions, remain based on the subjective symptoms reported by the headache patient and the exclusion of secondary headache causes. These broad diagnostic areas hide the heterogeneity of disease with different causalities. Thus, so far there are no clear human biomarkers for any of the primary headaches nor any unique pathophysiological insights into the molecular mechanisms of disease in patient sub-populations that can guide drug discovery and development. This review considers the history of drug development in primary headaches and discusses challenges to the discovery of innovative headache therapeutics.

2. Migraine treatment

The pathophysiological mechanism behind the initiation of migraine attacks is still not fully understood. Whether migraine is driven or caused by changes in the brain remains an area of discussion. PET studies showed the presence of activation in the brain stem of migraine patients (Afridi et al., 2005a,b; Bahra et al., 2001; Denuelle et al., 2007), and more recently imaging findings suggest that there may be preictal changes in the hypothalamus, which could alter signal processing in the trigeminal sensory and parasympathetic nuclei in the brain stem (Maniyar et al., 2014). Decreased inhibitory control of the sensory nuclei has also been suggested to be involved in lowering the migraine susceptibility threshold (Noseda and Burstein, 2013), and thereby differentially predispose a migraineur versus a non-migraineur to the initiation of a migraine attack in response to migraine triggers. In the case of migraine aura, there are visual disturbances that precede the migraine headache pain phase likely due to cortical spreading depression (CSD) (Olesen et al., 1981). The processes involved in the generation of headache pain during a migraine attack also remain the subject of intense debate. Perivascular sensory nerve fibers that densely innervate meninges are likely activated and sensitized during migraine attacks (Moskowitz and Macfarlane, 1993; Olesen et al., 2009) releasing pro-inflammatory neuropepetides and possibly initiating pain signal transmission. Central sensory relay neurons in the brainstem and thalamus may also become sensitized leading to cutaneous allodynia in some patients (Burstein et al., 2000; Goadsby et al., 2009a). The complexity of the pathophysiology of migraine may account for the variation in treatment response to single drug classes among patients and as a consequence there is a diverse pharmacology of drugs used in migraine treatment (Fig. 1 and Table 1).

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