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BIOLOGICAL SCIENCES FOR HEADACHE: PHARMACOLOGY

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Abstract

Headache treatment has been based primarily on experiences with nonspecific drugs such as analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), or drugs that were originally developed to treat other diseases such as beta blockers and anticonvulsant medications. A better understanding of the basic pathophysiological mechanisms of migraine and other types of headache has led to the development over the past two decades of more target specific drugs. Since activation of the trigeminovascular system and neurogenic inflammation are thought to play important roles in migraine pathophysiology, experimental studies modeling those events successfully predicted targets for selective development of pharmacological agents to treat migraine. Basically, there are two fundamental strategies for the treatment of migraine, abortive or preventative that is based to a large degree on the frequency of attacks. The triptans, which exhibit potency towards selective serotonin receptors expressed on trigeminal nerves, remain the most effective drugs for the abortive treatment of migraine. However, numerous preventative medications are currently available that modulate the excitability of nervous system, particularly the cerebral cortex. In this chapter, the pharmacology of commercially available medications as well as drugs in development that prevent or abort headache attacks will be discussed.

1) INTRODUCTION

Complex players such as genetic predisposition, environmental and intrinsic factors mediate headache, yet the exact sites and mechanisms of interaction remain obscure. Susceptibility genes for primary headache syndromes is a challenging research area that is likely to help identify specific targets for novel treatment strategies and facilitate our understanding of the interplay between genetic and environmental factors.

The trigeminovascular system plays a fundamental role in headache (Ray and Wolff 1940; Mayberg et al., 1981; Mayberg et al., 1984) in regard to peripheral sensitization (Strassman et al., 1996), neurogenic inflammation in the meninges (Dimitridau et al, 1992; Johnson and Bolay, 2006), and is also a predominant site of action for pharmaceutical agents such as triptans, ergots, neuropeptide antagonists, and non steroidal anti-inflammatory drugs (NSAIDs) (Buzzi et al, 1989; Buzzi et al, 1992; Durham and Russo, 2002; Kaube et al, 1993). Recent findings suggest that synaptic transmission between primary sensory trigeminal ganglia neurons and trigeminal nucleus caudalis (TNC) neurons within the

brainstem is a primary target of triptans and calcitonin gene-related peptide (CGRP) antagonists (Levy et al, 2004; Levy et al, 2005). Neurogenic inflammation (NI) is currently considered to be a phenomenon secondary to sensitization and/or activation of nociceptive neurons within the TNC (Goadsby and Hoskin, 1996; Kaube et al, 1993). Sensitization occurs not only in the peripheral structures but also develops in the brain stem and more rostral structures such as the thalamus and cerebral cortex (Burstein et al., 2000). Early administration of abortive treatments before central sensitization and cutaneous allodynia development has been reported to be most effective in treating migraine (Burstein & Jakubowski, 2004). Prostanoids, their receptors and terminal PGE synthases, particularly mPGES-1 along with COX-2 enzymes, are all important players in pain sensitization both in the periphery and in the CNS (Zeilhofer, 2007). After COX-2 inhibitors were withdrawn from market due to undesired side effects, such as cardiovascular toxicity (Bresalier, 2005), investigations have been directed to prostanoid receptors and mPGEs as new potential targets (Zeilhofer and Brune, 2006). The effect of pharmaceutical agents commonly used for abortive and prophylactic treatment other than NSAIDs on the development of sensitization has to be elucidated.

Cortical spreading depression (CSD), which is a pathophysiological correlate of aura, has stimulated a growing interest in regard to recent genetic and experimental findings. In familial hemiplegic migraine (FHM), hemiplegia is seen as an aura and inherited dominantly. Investigation of those families has yielded that ion channels or transporters such as CACNA1A and SCNA1 or Na⁺-K⁺ ATPase have been mutated (Ophoff et al 1996; DeFusco et al, 2003; Dichgans et al, 2005) in a way that results in release of excessive glutamate from neurons, reduced uptake of glutamate from the synaptic cleft into glia, and/or reduced buffering capacity to potassium ions (Moskowitz et al, 2004). The common result of all three identified mutations is the hyperexcitability and reduced threshold for CSD induction, which all probably contribute to the vulnerability of the brain to migraine attacks (Moskowitz et al, 2004). From the therapeutic perspective, the efficacy of certain anti-epileptic drugs in migraine patients and their action on excitability or even on CSD is noteworthy.

When administered chronically, several drugs currently used to treat epilepsy and migraines have been shown to be capable of reducing CSD frequency in rodents (Ayata et al., 2006). CSD is known to be a sufficient stimulus to activate the trigeminovascular system leading to activation of TNC neurons, and neurogenic edema and increased blood flow in the meninges (Bolay et al., 2002). Considering the treatment, the efficacy of abortive or prophylactic medication does not differ in migraine patients whether they have an aura or not. Therefore, the hypothesis that 'CSD may also underlie migraine without aura' is worthy of testing in clinical trials.

Headache treatment has been based primarily on experiences with nonspecific drugs such as analgesics, NSAIDs, or drugs that were originally developed to treat other diseases such as beta blockers and anticonvulsant medications. Somewhat surprisingly, we still do not fully understand their mode of action in alleviating migraine headache. Understanding the basic pathophysiological mechanisms of migraine has led to the development over the past two decades of target specific drugs such as triptans and CGRP antagonists. However, given the

limitations and side effects of many drugs it is obvious that there is still a need to develop more specific and effective medications to treat migraine and other headache disorders.

Another concept that has been changed for migraine treatment is the emphasis on prevention. Since recent evidence suggests that migraine is a chronic progressive disorder (Lipton and Pan, 2004), administration of prophylactic medication is now considered a necessary treatment option for more patients and for longer durations (Silberstein et al., 2004). Currently, the advantages or disadvantages of such an approach are not well defined.

Recent developments regarding the main groups of drugs effectively used in treating headaches are briefly summarized in the following sections. The pharmacology of selected serotonergic drugs, CGRP and other neuropeptide antagonists, prostanoids beyond cyclooxygenase inhibition, noradrenergic system and receptor blockade, and antiepileptic drugs will be discussed.

2) SEROTONERGIC AGONISTS

TRIPTANS

It was thought that migraine sufferers had a hereditary systemic perturbation of 5-HT metabolism and neurotransmission (Humphrey 1991; Ferrari and Saxena 1993). Earlier clinical evidence clearly demonstrated that the vasoconstrictors 5-HT and ergotamine, acting primarily through 5-HT receptors, were effective in aborting most migraine attacks. However, their therapeutic benefit was tempered by severe systemic side effects caused by these treatments. Thus, it was thought that design of a more selective drug that would selectively activate only 5-HT receptors in the cerebrovasculature would be even more effective in aborting migraine headache but would be without the negative systemic affects. The presence of mRNA and protein for the 5-HT_{1B/1D} class of 5-HT receptors has been demonstrated for human meningeal blood vessels and trigeminal ganglia neurons (Hamel, Fan et al. 1993; Longmore, Shaw et al. 1997). Specifically, immunolocalization studies have shown that the 5-HT_{1B} receptor, but not the 5-HT_{1D} receptor, is expressed on meningeal smooth muscle cells (Longmore, Shaw et al. 1997). Based on the current models of migraine pathology (Pietrobon 2005; Hargreaves 2007), activation of the 5-HT_{1B} receptors would cause vasoconstriction and, thus, could help restore normal vascular tone of these vessels during migraine. In contrast, although mRNA and protein for both 5-HT_{1B} and 5-HT_{1D} receptors was detected in the cell bodies of human trigeminal ganglia (Bouchelet, Cohen et al. 1996; Longmore, Shaw et al. 1997), only the 5-HT_{1D} receptors appear to be expressed on peripheral and central projecting trigeminal nerve fibers (Longmore, Shaw et al. 1997). Thus, activation of the human 5-HT_{1D} receptor is thought to be primarily responsible for mediating repression of stimulated neuropeptide release from human trigeminal nerve terminals and activation of second order neurons. These inhibitory effects on trigeminal nerve activity would promote normalization of blood vessel diameter and also inhibit release of neuropeptides that are responsible for transmitting nociceptive stimuli to the CNS.

Sumatriptan (3-[2-dimethylamino]ethyl-N-methyl-1H-indole-5-methane sulphonamide) (GlaxoSmithKline) was the first selective 5-HT_{1B/1D} agonist that was specifically designed for the acute treatment of migraine headache. At least 14 different subtypes comprising 7

subfamilies of distinct serotonergic receptors have been identified (Boess and Martin 1994; Barnes and Sharp 1999). Based on numerous animal and clinical studies, the 5-HT₁ class of receptors is now regarded as the most relevant for migraine therapy (Longmore, Dowson et al. 1999). Data generated from extensive pharmacological studies has demonstrated that sumatriptan is a potent agonist of the human 5-HT_{1B/1D/1F} receptors (Beattie and Connor 1995; Longmore, Dowson et al. 1999). It exhibits highest affinity for the 5-HT_{1B} and 5-HT_{1D} receptors, with slightly lower affinity for the 5-HT_{1F} receptors while showing only weak affinity for the 5-HT_{1A} and 5-HT_{1E} receptors. Importantly, sumatriptan displays only weak affinity at other 5-HT receptors (5-HT_{2A/3/4/5/7}) and other non-5-HT₁ receptors, such as the adrenergic, dopamine, and muscarinic receptors. Based on the success of sumatriptan in migraine therapy, several other drugs, collectively now known as the triptans, were designed with selectivity towards the 5-HT_{1B/1D} receptors that could overcome some of the potential shortcomings of sumatriptan (Ferrari 1998; Longmore, Dowson et al. 1999). For example, the newer drugs offer greater bioavailability, longer plasma half-life, faster absorption, and increased lipophilicity, leading to greater brain penetration than reported for sumatriptan. The new so-called second-generation triptan drugs include naratriptan (GlaxoSmithKline), zolmitriptan (Zeneca), rizatriptan (Merck & Co), eletriptan (Pfizer), frovatriptan (Vanguard Medica), almotriptan (Almirall/Pharmacia & Upjohn), and avitriptan (Bristol-Meyers Squibb). Basically, the triptans are similar with respect to their pharmacology, efficacy, and safety. The drug LY-334370 (Eli Lilly & Co) is reported to be highly selective for the 5-HT_{1F} receptor and to cause inhibition of dural protein plasma extravasation (Johnson, Schaus et al. 1997). However, the effectiveness of this drug in migraine therapy was never established in larger clinical trials due to its withdrawal after adverse events were noted in dogs. While clinical data clearly supports the effectiveness of the triptans in aborting migraine, there is still much debate focused on which triptan should be used to treat other types of headache such as cluster headaches and menstrual migraine. Despite the success of these drugs as acute treatments of migraine, not all patients are responsive to the triptan drugs. In addition, since all triptan drugs are known to have vasoconstrictor activity, they are contraindicated in patients with vascular disease (Longmore, Dowson et al. 1999). This practice is highly recommended because of the possibility of serious cardiovascular events, such as myocardial infarction (Mueller, Gallagher et al. 1996), cardiac arrhythmia (Ottervanger, van Witsen et al. 1994), and stroke (Luman and Gray 1993; Cavazos, Caress et al. 1994). Thus, although the triptans are superior to other drugs for the acute treatment of migraine, there remains a significant number of migraineurs who are unable to be successfully treated with these drugs.

The effectiveness of sumatriptan and other triptans as acute antimigraine therapies has been proposed to be due to three separate pharmacological actions at distinct sites within the trigeminovascular system (Ferrari 1998; Hargreaves and Shepherd 1999). These actions include vasoconstriction of meningeal and cerebral blood vessels, inhibition of neuropeptide release from perivascular trigeminal nerves, and central effects involving decreased pain transmission (Bolay and Moskowitz 2005; Pietrobon 2005). In addition, a potential fourth site of action has been suggested that involves triptan inhibition of release of CGRP and possibly other neuropeptides from trigeminal neuron cell bodies that are localized in the ganglia (Zhang, Winborn et al. 2007). After much research, the most important site of triptan

action remains unknown but may very well function at some degree at all four levels along the trigeminovascular system to abort the pain and associated symptoms of migraine.

The vascular mechanism of the triptans has been shown to involve constriction of painfully distended intracranial blood vessels via activation of 5-HT_{1B} receptors on vascular smooth muscle cells (Friberg, Olesen et al. 1991; Humphrey and Feniuk 1991). In a study utilizing angiography, sumatriptan was also shown to cause constriction of human meningeal (dural) blood vessels (Henkes, May et al. 1996). The neurogenic mechanism of triptan action is mediated by inhibiting the secretion of the vasoactive neuropeptides CGRP and SP from perivascular trigeminal nerves via activation of the 5-HT_{1B/1D} receptors (Moskowitz 1992; MacLeod, Street et al. 1997; Williamson, Hill et al. 2001) and possibly 5-HT_{1F} receptors (Johnson, Schaus et al. 1997). The central mechanism by the brain-penetrant triptan drugs involves inhibition of nociceptive activity in the brainstem trigeminal sensory nuclei (Goadsby and Edvinsson 1994; Shephard, Williamson et al. 1995; Goadsby and Hoskin 1996; Cumberbatch, Hill et al. 1997). This central action is likely to be mediated by an inhibition of neuropeptide and/or glutamate release from central-projecting trigeminal afferent fibers (Cumberbatch, Hill et al. 1998) at the level of the trigeminal nucleus caudalis (Jenkins, Langmead et al. 2004; Levy, Jakubowski et al. 2004). Consistent with this proposed mechanism, expression of the immediate early gene c-fos, a marker of neuronal activation within the cephalic nociceptive system, is attenuated by triptan drugs in the trigeminal nucleus caudalis following noxious meningeal stimulation (Nozaki, Boccalini et al. 1992). A very interesting recent finding was that the effect of triptans involves the activation of 5-HT_{1D} receptors on pain-responsive trigeminal primary afferents (Ahn and Basbaum 2006). In this way, membrane expression of 5-HT_{1D} receptors on trigeminal nerves is increased under pathological conditions making them more readily available for triptan activation. Hence, based on these findings it is likely that the therapeutic benefit of triptans involves modulation of the 5-HT_{1D} receptors. Finally, recently published findings support the notion that triptans can function at the level of the cell body of trigeminal ganglia neurons by blocking autocrine regulation of CGRP synthesis. While it is known that CGRP can be released from neuronal cell bodies in response to inflammatory stimuli, it was not known how CGRP might function at the level of the ganglia. In this recent study, evidence was provided to demonstrate that activation of CGRP receptors expressed on trigeminal neurons leads to increased CGRP synthesis (Zhang, Winborn et al. 2007). Thus, the release of CGRP from cell bodies localized within the ganglia would be able to promote further production of CGRP. Treatment with triptans would likely block this effect since 5-HT_{1D} receptors are known to be expressed on the cell body of trigeminal neurons.

Based on pharmacological data, sumatriptan and other currently used triptan anti-migraine drugs exhibit potency and selectivity primarily towards the 5-HT_{1B} and 5-HT_{1D} receptors. The 5-HT_{1B} receptors were first identified in rat brain by 5-HT-binding studies (Pedigo, Schoemaker et al. 1981).. However, data from binding studies in humans, dogs, and guinea pigs clearly demonstrated the existence of another class of 5-HT₁ receptors, which was termed 5-HT_{1D} receptors and found to be quite distinct pharmacologically from the 5-HT_{1B} receptors (Heuring and Peroutka 1987; Hoyer et al., 1988; Hoyer and Middlemiss 1989;). While both humans and rats are known to express the 5-HT_{1B} and 5-HT_{1D} receptor

genes, the pharmacology of these receptors is reported to be very similar in human, but quite distinct, in the rat (Boess and Martin 1994).

All of the identified 5-HT receptors, with the exception of 5-HT₃ receptors, are known to be G-protein-coupled receptors that contain seven membrane-spanning hydrophobic segments and specific recognition domains (Boess and Martin 1994). The G-protein-coupled receptor family is the largest and most complex group of integral membrane proteins involved in signal transduction. These receptors are activated by a diverse array of external stimuli that includes growth factors, vasoactive peptides, neurotransmitters, and hormones (Wess 1997). Traditionally, activation of 5-HT₁ receptors involved in migraine therapy has been viewed as being coupled to an inhibition of adenylate cyclase via pertussis toxin-sensitive Gi/o-proteins, leading to a decrease in intracellular cyclic AMP (cAMP) levels (Boess and Martin 1994). However, data from studies using cultured trigeminal ganglia neurons showed that sumatriptan could not inhibit forskolin-stimulated adenylate cyclase activity or forskolin-induced cAMP accumulation (Durham and Russo 1999). In this study, the same cultures assayed for cAMP were shown to exhibit sumatriptan-mediated repression of CGRP release. Thus, these data provide evidence that cultured trigeminal neurons express functional 5-HT₁ receptors, as demonstrated by their response to sumatriptan, but do not couple to cAMP. In agreement, other investigators have also reported that terminal hippocampal neuron 5-HT₁ receptors may not be coupled to Gi/o-proteins and decreased cAMP levels (Blair 1991). Activation of human 5-HT₁ receptors has also been reported to couple to increases in intracellular Ca²⁺ levels. (Zgombick, Borden et al. 1993; (Adham, Borden et al. 1993). Since the increase in Ca²⁺ levels observed in these studies was blocked by pertussis toxin treatment, recruitment of Gi/Go-proteins was likely involved in mediating the Ca²⁺ increases. More recently, activation of 5-HT₁ receptors has been shown to couple to increased Ca²⁺ levels, but by a different mechanism and with very different kinetics than previously reported. Rather than causing a transient Ca²⁺ increase, activation of 5-HT₁ receptors in cultured trigeminal neurons was shown to cause a prolonged submicromolar increase in intracellular Ca²⁺ levels (Durham and Russo 1999). Importantly, the increase in intracellular Ca²⁺ was shown to block the stimulated release of CGRP from trigeminal neurons. Together, there is evidence that activation of 5-HT₁ receptors can lead to changes in cAMP and intracellular calcium levels, which are likely involved in mediating the inhibitory affects of anti-migraine drugs that bind 5-HT₁ receptors.

ERGOTS

The ergot alkaloids, ergotamine and its derivative, dihydroergotamine (DHE) are effective for the treatment of moderate to severe migraine but suffer from lack of poor bioavailability. A unique characteristic of DHE and other ergot alkaloids is that their biological activity does not directly correlate with their plasma concentrations. DHE exhibits affinity for several types of receptors including serotonin, adrenergic, and dopamine receptors (Saper and Silberstein 2006). While the exact mechanism of action of DHE in treating migraine is not known, it is thought to involve its ability to bind and activate 5-HT_{1D} receptors present on trigeminal nerves. Although sumatriptan was shown to be superior to DHE in the acute relief of the headache associated with migraine, headache recurrence was reported twice as often

with sumatriptan use (Winner, Ricalde et al. 1996). This beneficial affect of DHE is likely due to its long duration of pharmacological activity as compared to the triptans.

3) CALCITONIN GENE-RELATED PEPTIDE (CGRP) RECEPTOR ANTAGONISTS

The neuropeptide calcitonin gene-related peptide (CGRP) is implicated in the underlying pathology of migraine and cluster headache. In humans, CGRP exists in two forms, α -CGRP and β -CGRP, which differ by three amino acids yet exhibit similar biological functions (Amara, Arriza et al. 1985; Steenbergh, Hoppener et al. 1985). The 37-amino acid neuropeptide α -CGRP arises from alternative processing of the primary transcript to yield the hormone calcitonin in thyroid C-cells and CGRP in a large number of neurons of the peripheral and central nervous systems (Rosenfeld, Mermod et al. 1983; Fischer and Born 1985; Steenbergh, Hoppener et al. 1985). β -CGRP is encoded by a different gene that is highly homologous to the calcitonin-CGRP gene.

Immunohistological studies have demonstrated that α -CGRP is preferentially expressed in sensory neurons and its concentration is 3- to 6-fold higher than that of β -CGRP (Mulder, Ghatei et al. 1988). The role of α -CGRP will be the focus of this discussion since this isoform is predominant in trigeminal ganglia (Amara, Arriza et al. 1985). Furthermore, dilation of human cerebral arteries is mediated largely by α -CGRP (Jansen-Olesen, Mortensen et al. 1996). For convenience, α -CGRP will simply be referred to as CGRP.

The important role of CGRP in migraine pathology is supported by both clinical and experimental evidence. CGRP is the most potent vasodilatory peptide in the cerebral circulation (Brain, Williams et al. 1985; McCulloch, Uddman et al. 1986) and it is expressed in trigeminal ganglia neurons that innervate all the major cerebral blood vessels, as well as the pain-sensing meningeal blood vessels (O'Connor and Van der Kooy 1988; van Rossum, Hanisch et al. 1997). Functional studies have demonstrated that exogenous CGRP causes vasodilation of cerebral arteries in vitro and in situ (Jansen-Olesen, Mortensen et al. 1996). In addition to causing vasodilation, CGRP has been reported to cause dural mast cell degranulation and release of histamine, and may be involved in mediating neurogenic inflammation by facilitating plasma leakage from meningeal vessels (Ossowski and Edvinsson 1997). In addition, CGRP is likely involved in the transmission of painful stimuli from intracranial vessels to the central nervous system (Cumberbatch, Hill et al. 1998). In animal models of neurogenic inflammation, CGRP levels have also been shown to be elevated in the sagittal sinus following chemical or electrical stimulation of the trigeminal ganglion nerve in the rat (Buzzi, Carter et al. 1991; Knyihar-Csillik, Tajti et al. 1995) and the cat (Zagami, Goadsby et al. 1990).

Furthermore, excitation of afferent perivascular nerve fibers was shown to cause elevations in rat plasma CGRP levels (Buzzi, Carter et al. 1991) that are comparable with increases reported in migraine patients during an attack (Goadsby and Edvinsson 1993). Thus, release of CGRP and other neuropeptides from trigeminal nerves is thought to mediate neurogenic inflammation within the meninges that contributes to generation of the severe cerebral pain experienced during migraine attacks. Interestingly, chemical and electrical stimulation of

dural afferents was reported to cause a significant increase in the amount of CGRP, but not SP, released from trigeminal nerves (Ebersberger, Aeverbeck et al. 1999). Thus, while other neuropeptides, such as SP and neurokinin A, are involved in regulation of the cerebrovasculature, their roles in migraine are not clear (Edvinsson and Goadsby 1994; Buzzi, Bonamini et al. 1995).

Data from clinical studies have shown that serum levels of CGRP, obtained from the external jugular vein, are elevated in patients during migraine with and without aura as well as cluster headaches (Goadsby and Edvinsson 1993; Edvinsson and Goadsby 1994; Goadsby and Edvinsson 1994; Fanciullacci, Alessandri et al. 1995). Further evidence for a role of CGRP in migraine comes from clinical studies in which sumatriptan was shown to decrease elevated CGRP levels in migraine patients, coincident with relief of headache pain (Goadsby and Edvinsson 1991). Furthermore, these data provide evidence that receptor antagonist molecules, which selectively bind to CGRP receptors to prevent their function, should be effective in migraine treatment by blocking the pathophysiological activities of CGRP.

The physiological effects of CGRP are mediated via activation of CGRP receptors, which are divided into two classes, CGRP1 and CGRP2 (Amara, Arriza et al. 1985; Poyner, Sexton et al. 2002). Functional CGRP receptors are composed of the calcitonin-like receptor (CLR receptor) and a single transmembrane domain protein called receptor activity modifying protein type 1 (RAMP1). The first CGRP receptor antagonists were C-terminal truncated fragments of the CGRP peptide (Chiba, Yamaguchi et al. 1989). The CGRP1 receptors are reported to be more sensitive to the peptide antagonist CGRP₈₋₃₇ than CGRP2 (Quirion, Van Rossum et al. 1992). CGRP₈₋₃₇, which includes all but the first seven amino acids of normal CGRP, functions as an antagonist of CGRP receptors by blocking binding of endogenous full-length CGRP. Although CGRP₈₋₃₇ has been demonstrated to inhibit vasodilation and neurogenic inflammation in animal models, it has not proven clinically effective due to its short half-life and lack of potency *in vivo*. Other truncated CGRP analogs that exhibit higher affinity for CGRP1 receptors than CGRP₈₋₃₇ have been developed but have also not proven useful in clinical studies because of the same limitations (Rist, Lacroix et al. 1999). However, results from physiological studies using truncated forms of CGRP have provided evidence that blockage of CGRP receptors by small nonpeptide molecules should be beneficial in treating migraine.

The introduction of the antimigraine drug sumatriptan not only changed the way in which migraine patients were managed, but also provided valuable insight into the underlying mechanisms involved in migraine pathology (Mathew 2001; Goadsby, Lipton et al. 2002). Sumatriptan, which was specifically designed for migraine therapy, remains a standard by which other drugs for acute treatment of migraine, including the newer triptan drugs, are evaluated. Triptan induced activation of 5-HT₁ receptors inhibits vasodilation of intracranial vessels, and blocks neurogenic inflammation and central transmission of nociceptive stimuli by inhibiting the release of CGRP, other neuropeptides, and glutamate from trigeminal nerves (Hargreaves 2007). Unfortunately, the vasoconstrictor action of triptans is a serious, unwanted side effect that precludes their use in some migraine patients (Visser, Jaspers et al. 1996). In fact, all triptans are contraindicated in patients with established cardiovascular disease and are to be used cautiously in patients in who unrecognized coronary artery

disease is likely. In addition, about one-third of patients do not respond to sumatriptan treatment, and there is a high recurrence rate associated with all triptans (Geraud, Keywood et al. 2003). To offer an improved safety profile over the triptans, a drug would need to effectively decrease CGRP release from trigeminal neurons, thus inhibiting vasodilation of meningeal vessels and nociceptive transmission, but lack coronary vasoconstrictor activity.

The rationale for developing novel CGRP receptor antagonists to treat migraine was based on data obtained from studies on the mechanisms of triptans and evidence that administration of human CGRP can induce migraine like symptoms in susceptible individuals. Doods and colleagues (Doods, Hallermayer et al. 2000) identified a potent and highly specific antagonist to human CGRP receptors termed olcegepant (Boehringer Ingelheim; . Results from a phase II clinical trial for the treatment of migraine have been published (Olesen, Diener et al. 2004). Compounds 1 and 2, truncated analogs of olcegepant, also exhibit high affinity for human CGRP receptors, but exhibited lower potencies than olcegepant (Mallee, Salvatore et al. 2002). The specific affinities of these three antagonist molecules are dependent on residues within the extracellular region of RAMP1 rather than the receptor protein CL. Thus, it appears that the non-peptide antagonists function by directly competing for the binding site of the endogenous ligand, CGRP. Blockage of CGRP1 receptors expressed on cerebral arteries, meningeal blood vessels, and second-order sensory neurons would inhibit the vasodilatory and nociceptive effects of CGRP.

The ability of olcegepant to function as an antimigraine agent was supported by results suggesting that the drug could inhibit the vasodilatory effect of CGRP released following stimulation of the trigeminal ganglion (Doods, Hallermayer et al. 2000). Data from a published clinical proof-of-concept study by Olesen and co-workers (Olesen and Jansen-Olesen 2000) demonstrated the effectiveness and safety of olcegepant for acute treatment of migraine. The response rate of > 60% (pain-free at 2 h) is similar to values reported for oral triptans (Ferrari, Roon et al. 2001). It is likely that even higher response rates, as recently reported for the triptans, can be achieved if olcegepant is administered during the mild phase of a migraine attack before trigeminal nerve activation (Burstein, Collins et al. 2004). Notably, no cardiovascular side effects, for example, changes in basal blood pressure or heart rate, have been reported following administration of olcegepant (Kapoor, Arulmani et al. 2003). The lack of vasoconstrictor activity may prove to be a major advantage for using CGRP receptor antagonists to treat migraine. Clinically, it is important to determine whether patients who fail to respond to triptans might be successfully treated by olcegepant. This may be doubtful if the antimigraine effect of triptans is primarily mediated through inhibition of CGRP release from trigeminal nerves, and olcegepant blocks CGRP receptor function.

Although olcegepant has been shown to be effective in treating migraine attacks, a severe limitation is that this compound has to be delivered via intravenous injection. It is encouraging that potent oral CGRP receptor antagonists are now under investigation for the treatment of migraine. In particular, the CGRP receptor antagonist, MK-0974, reported to exhibit good oral bioavailability, is a promising candidate (Paone et al., 2007). MK-0974, telcagepant was shown in a phase II clinical study to be effective and generally well-

tolerated for treating moderate to severe migraine attacks with a primary endpoint of pain relief at 2 hours (Ho et al., 2008). Generally, the effective MK-0974 doses were comparable to those of rizatriptan. The incidence of the most often reported adverse events for MK-0974, which included nausea, dizziness, and somnolence, were similar to the placebo group. Pharmacological studies have provided evidence that MK-0974 is a highly selective, potent oral antagonist of the human CGRP receptor (Salvatore et al., 2008). In the same study, MK-0974 was shown to inhibit capsaicin-induced dermal vasodilation mediated by CGRP in rhesus monkey pharmacodynamic assay. Phase III clinical studies are underway to further evaluate the effectiveness of this novel class of CGRP receptor antagonist molecules.

There are several potential sites of action for CGRP antagonists along the trigeminovascular pathway. Since human cerebral vessels have been demonstrated to express functional CL receptor and RAMP1 proteins (Moreno, Cohen et al. 1999; Oliver, Wainwright et al. 2002), blockage of these CGRP receptors on smooth muscle cells would inhibit the dilation of major cerebral vessels. Indeed, olcegepant reportedly reversed the effects of CGRP-induced dilation of human middle cerebral and middle meningeal arteries (Moreno, Abounader et al. 2002; Moreno, Terron et al. 2002). In addition, CGRP antagonists may block neurogenic inflammation within the meninges by inhibiting dilation of meningeal vessels, a key initiating event proposed in migraine. The drug should also be able to inhibit mast cell degranulation and subsequent release of histamine and other pro-inflammatory agents. Another likely target for a CGRP antagonist is CGRP receptors on second-order sensory neurons within trigeminal nuclei in the caudal brain stem and upper cervical spinal cord (Levy, Jakubowski et al. 2004). Competitive inhibition of these receptors would prevent activation of nociceptive neural pathways and thus block sensitization of second-order neurons during migraine, which contribute to the intensification of pain reported during an attack. In addition, inhibition of the trigeminovascular system would also be expected to diminish the allodynic effects and autonomic-mediated symptoms commonly associated with migraine (Malick and Burstein 2000). Results from a randomized clinical trial of olcegepant demonstrated the effectiveness of the drug at decreasing or alleviating migraine pain, but also importantly reported patient improvement with respect to nausea, photophobia, phonophobia and functional capacity (Olesen, Diener et al. 2004). Finally, it will be of importance to determine whether a CGRP antagonist could function at the level of the trigeminal ganglia to inhibit peripheral sensitization since trigeminal ganglia neurons and satellite glial cells are reported to express functional CGRP receptors (Thalakoti, Patil et al. 2007; Zhang, Winborn et al. 2007).

In summary, based on experimental and clinical studies, CGRP is believed to play an important role in the generation of pain during migraine attacks. The CGRP receptor antagonist olcegepant has been demonstrated to be effective in treating migraine attacks. The apparent lack of coronary vasoconstrictor activity would be a major advantage of using this drug instead of triptans for the acute treatment of migraine, especially in patients with a history of cardiovascular disease. A major challenge will be to provide a more easily administered formulation of the antagonist, preferably an oral tablet or nasal spray, as has been developed for the delivery of triptans. The therapeutic potential of olcegepant, telcagepant and possibly other CGRP receptor antagonists appears favorable for treating

migraine as well as cluster headache since serum CGRP levels are greatly elevated in cluster headache patients.

4) PROSTANOIDS AND INFLAMMATION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs worldwide for mild and moderate pain including headache. A well known member of this group, acetylsalicylic acid (ASA), was first synthesized in 1899 by Felix Hoffman. However it took 80 years before it was discovered that aspirin acts as an inhibitor of cyclooxygenase (COX), preventing the formation of prostaglandins (PG) from arachidonic acid (Vane, 1971).

Prostanoids are a group of lipid mediators that consist of the prostaglandins and thromboxanes and derive from membrane phospholipids. Phospholipase A2 releases arachidonic acid from membrane phospholipids in response to cell stimulation. Arachidonic acid is then subsequently converted to PG endoperoxidases in a two step reaction, first to PGG2 and then PGH2 by the action of COX enzymes. PGH2 is converted to various prostaglandins by tissue specific prostaglandin synthases as determined by cell type (Smith et al., 2000; Garavito et al., 1999). Platelets catalyze the formation of TXA₂ from endoperoxide, whereas vascular endothelium produces prostacyclin (PGI₂). Once formed, prostanoids are immediately released from the cells and act in the vicinity of their sites of production via activation of G protein coupled receptors (Narumiya et al., 1999).

NSAIDs, which inhibit COX enzymes and thus prevent the synthesis of prostaglandins, are known to exhibit various analgesic, anti-inflammatory, and antipyretic properties. The analgesic and anti-inflammatory properties of NSAIDs do not necessarily show correlation, as in the case of acetaminophen (McCormack and Brune, 1994).

CYCLOOXYGENASES

COXs have different types of isoforms. COX-1 and COX-2 are about 60% identical in terms of molecular structure but differ in terms of temporal and spatial expression and function. COX-1 is a constitutively expressed enzyme present in most cells involved in physiological reactions like vascular endothelium, platelets and epithelial cells of the renal tubules (Smith et al., 2000; O'Neill GP & Ford-Hutchinson, 1993). Prostaglandins formed by COX-1 are important in protecting the gastric mucosa and in maintaining the platelet and renal function. COX-2 expression is almost undetectable in most tissues under normal physiological conditions but can be induced by 10- to 80-fold by inflammation. Various factors including neurotransmitters, growth hormones, pro-inflammatory cytokines and lipopolysaccharide induce COX-2 expression (Smith et al., 2000; O'Banion et al., 1999). However, there are exceptions to the expression pattern of the COX enzymes. For example, COX-1 levels are typically quite stable but can be induced under stressful conditions and in the absence of inflammation COX-2 is constitutively expressed in the CNS and renal cortex serving normal physiological functions (Morteau, 2000; Schwab et al., 2000; Yaksh et al, 2001). Acetaminophen (paracetamol in Europe) has long been considered to mediate analgesic and antipyretic actions centrally through COX-3 isoenzyme, a splice variant of COX-1 and to be devoid of significant inhibition of peripheral prostanoids (Botting, 2000; Chandrasekharan et

al., 2002; Schwab et al., 2003). Recent studies failed to exhibit the existence of centrally acting COX-3 isoenzyme and demonstrated peripheral anti-inflammatory action of acetaminophen that displays an 4-fold selectivity for inhibition of COX-2 both in vitro and in vivo (Li et al, 2008; Hinz et al, 2008).

Generally, NSAIDs are considered competitive reversible inhibitors of COX with the exception being ASA, which inhibits all isoforms irreversibly.

Based on their inhibitory effects on COX, NSAIDs can be classified as (Samad et al., 2002; Botting, 2003); *a) nonspecific COX inhibitors*: Inhibits both COX-1 and COX-2 (Most of NSAIDs, ibuprofen, meclofenamate), *b) selective COX-1 inhibitors*: Indomethacin, piroxicam, sulindac, *c) selective COX-2 inhibitors*: Inhibits COX-2 in clinical therapeutic doses, also inhibits COX-1 in higher doses (meloxicam, diclofenac, nimesulid, etodolac), *d) specific COX-1 inhibitors*: Inhibits COX-1 without inhibiting COX-2 (no available drug except low doses of aspirin), *e) specific COX-2 inhibitors*: Inhibits COX-2 without inhibiting COX-1, Coxibs (celecoxib, rofecoxib, valdecoxib, etoricoxib, parecoxib, acetaminophen).

Specific COX-2 inhibitors seemed to be better tolerated analgesics having similar therapeutic efficacy with conventional NSAIDs but with reported lower gastric side effects (Katori and Majima, 2000). Rofecoxib and lumiracoxib reduced the incidence of gastrointestinal bleeds and ulcerations by approximately 60% compared to non-selective NSAIDs. However, a few years ago, clinical studies suggested that rofecoxib had higher cardiovascular and renal toxicity compared to naproxen (Bombardier et al, 2000). Thereafter, rofecoxib was withdrawn from the market due to the doubled risk of myocardial infarction following long-term administration (Bresalier et al., 2005). It was proposed that there might be a slight tendency towards a drug-induced hypercoagulable state (Solomon et al, 2004). Subsequently, research has focused on new therapeutic targets in the prostanoid production (Zeilhofer and Brune, 2006), including ten different terminal prostaglandin synthases and at least eight different prostanoid receptors activating various signal cascades in different types of cells.

PROSTAGLANDIN SYNTHASES

Recent studies indicate prostaglandin synthases are an important therapeutic target for both inflammation and pain, since at least ten different types of enzymes have been discovered to convert prostaglandin precursors into biologically active prostanoids. Regarding its pivotal role in pain, PGE₂ synthases have received much recent attention compared to the others (Murakami et al., 2000).

PGE synthases have several forms, two membrane bound forms, called microsomal PGE synthase-1 (mPGES-1), mPGES-2, and one cytosolic form, called cPGES. mPGES-1 is associated with COX-2, and its expression is induced by inflammatory stimuli in both peripheral and central nervous system (Murakami et al., 2000; Zeilhofer and Brune, 2006). mPGES-2 and cPGES are constitutively expressed and while the first one is associated with both COX isoenzymes, the latter shows preferential coupling to COX-1. In accordance with preferential association with mPGES-1 to COX-2, mPGES-1 knockout mice display no

PGE₂ increase after induction of COX-2 with lipopolysaccharide, and significantly reduced pain associated behavior indicating the important role of mPGES-1 in inflammation and pain response (Kamei et al., 2004). Hence, inhibition of mPGES-1, which is responsible of the synthesis of PGE₂, might be an effective analgesic with lower cardiovascular and renal side effects comparable with coxibs. Therefore prostaglandin synthases seem to be appropriate targets for novel and potentially better-tolerated analgesics.

PROSTANOID RECEPTORS

Both desired and unwanted effects of NSAIDs are mediated by prostanoid receptors, though the types of the receptor as well as its tissue and cell distribution are major determinants of their ultimate function.

Prostanoid metabolites of arachidonic acid PGD₂, PGE₂, PGF₂, PGI₂ and TXA₂ exert their actions via interaction with specific plasma membrane G protein coupled receptors, called DP, EP, FP, IP and TP respectively (Tsuboi et al., 2002; Narumiya et al, 1999; Sugimoto & Narumiya, 2007). EP receptors are classified further into EP₁, EP₂, EP₃, and EP₄ subtypes, each having different pharmacologic properties. Various tissues and cell types express prostanoid receptors, and activation of receptor subtype influences the function (Sugimoto & Narumiya, 2007). For example, in smooth muscle cells DP and IP receptors mediate relaxation whereas FP and TP receptors are functionally associated with contractile responses. While EP₁ and EP₂ receptors are present in the stomach, kidney, uterus and nervous system, EP₃ and EP₄ are widely expressed in the body (Tsuboi et al., 2002; Sugimoto & Narumiya, 2007). Consistent with the role of PGE₂ in peripheral sensitization, EP₁, EP₃ and EP₄ receptor mRNAs are expressed in primary sensory neurons and trigeminal ganglia (Southall & Vasco, 2001). Post receptor events are determined according to the G protein subtype that each prostanoid receptor is coupled. Stimulation of adenyl cyclase via G_s proteins leads to increases in cyclic adenosine monophosphate (cAMP) (EP₂, EP₄, EP_{3C,D}, DP and IP) while activation of G_i leads to a decrease in intracellular cAMP (EP₁, EP_{3A}, FT and TP). EP₁ and EP₃ receptors mediate smooth muscle contraction by inhibition of cAMP via G_q/G_i proteins (Negishi et al., 1995). In contrast, EP₂ and EP₄ receptors mediate relaxation in the vascular smooth muscle (Tsuboi et al., 2002; Sugimoto & Narumiya, 2007).

Among the PGE₂ receptors EP₁ is the main receptor responsible for mucosal protection. Recent data from EP receptor-deficient mice suggests that reduced activation of EP₁ and EP₃ receptors underlies the ulcerogenic effects of COX inhibitors (Suzuki et al, 2001). Cardiovascular risk of COX-2-selective agents (Teveder and Geisslinger, 2006) might arise due to the alteration of thromboxane and PGI₂ where the first one is notable with vasoconstrictive and proaggregatory properties while the latter with vasodilating and antiaggregatory properties (Audoly et al., 1999). It should be kept in mind that an increase in blood pressure that is seen with almost all COX inhibitors may predispose patients with a risk for cardiovascular complications. Albeit, renal function abnormalities are basically associated with PGIS knock-out mice, EP₂ and EP₄ receptor-deficient mice also display dysregulation of blood pressure (Kennedy et al., 1999).

EP receptors have been shown to be localized in trigeminal ganglion neurons where the stimulation results in CGRP release (Jenkins et al., 2001; Vasco et al., 1994). Moreover, EP₄ receptors mediate PGE₂-induced dilation of middle cerebral artery (Davis et al., 2004). It is likely that prostaglandins, particularly PGE₂, may be involved in the pathology of migraine headache and sensitization of neurons by stimulating CGRP release from trigeminal afferents and also mediating vascular responses

PROSTANOIDS AND PAIN

Prostanoids produced both in the peripheral structures and in the central nervous system particularly in the spinal cord play a role in the development of pain. The prostaglandins such as PGE₁ and PGE₂ do not directly activate nociceptor and mediate pain transmission but they contribute to hyperalgesia peripherally by sensitizing nociceptive sensory nerve endings to other mediators (like histamine and bradykinin) and by sensitizing nociceptors to respond to non-nociceptive stimuli (allodynia) (Bolay and Moskowitz, 2002; Woolf and Salter, 2000). Prostanoids play a significant role in peripheral sensitization through EP receptor coupled post receptor events such as protein kinase A mediated phosphorylation of Nav1.8 sodium channel (Waxman et al., 1999) and TRPV1 nonselective cation channels (Moriyama et al., 2005), which are directly involved in depolarization of nociceptor terminals (Figure 1). Thereby prostanoids function to reduce the firing threshold and increase excitability to consecutive nociceptive stimuli such as heat, protons, bradykinin, and prostanoid itself. Prostaglandins also have direct actions on the spinal cord to enhance nociception, notably at the terminals of sensory neurons in the dorsal horn (Zeilhofer, 2007; Reinhold et al., 2005). This effect is mediated by increasing the release of glutamate and substance P from primary nociceptive afferents (Hingten & Vasco, 1994; Southall & Vasco, 2001), that depolarize second order nociceptive neurons in the dorsal horn, and inhibiting the glycine-mediated inhibition (Baba et al., 2001; Ahmadi et al., 2002). Inhibition of glycine receptor occurs through EP₂ receptor coupled PKA phosphorylation of glycine receptor isoform containing $\alpha 3$ subunit that is specifically expressed in superficial nociceptive layers (Harvey, 2004). Prostanoids, as briefly mentioned above, modulate other receptors involved in depolarization such as tetrodotoxin Na⁺ channels, TRPV1 channels or strychnine-sensitive glycine receptors in a way to enhance nociception.

Prostaglandins have both pro- and anti-inflammatory properties. The specific response is determined by prostanoid produced, specific receptor, cell type, and the time course of inflammatory signal (Zeilhofer, 2007). For example PGE₂ is generally considered as a pro-inflammatory molecule acting on EP₂ receptor coupled to cAMP increase (Zeilhofer, 2007; Samad et al., 2002). Prostanoids may alternatively modulate anti-inflammatory action by binding to peroxisome proliferator- activated receptor (PPAR) γ nuclear hormone receptor (Rotondo, 2002). Depending on the time course of inflammation prostanoid production has two distinct phases (Balsinde and Dennis, 1996). The first phase of arachidonic acid and prostanoid release occurs within minutes of stimulation. However, late phase requires synthesis of new proteins such as PLA₂, COX2 and PGES. While arachidonic acid generated during the initial phase is metabolized by constitutively expressed COX-1/COX-2 enzymes, it is a main substrate for COX2 in the delayed phase response yielding prostanoids such as PGE₂ (Samad et al., 2002; Tegeder et al., 2001)

COX-2 is upregulated following inflammation and direct neural input, and also humoral factors play a role in this process. Inflammatory proteins, cytokines released into the circulation such as interleukin 6 (IL-6), triggers the formation of IL-1 β , the production of COX-2 and PGE₂ in the CNS (Samad et al., 2001). COX-2 expression seen throughout the CNS including the thalamus and cerebral cortex bilaterally is a humoral response and cannot be prevented by the dissection of the nerves carrying the pain from the affected site (Samad et al., 2001). COX-2 is produced in several cells such as neurons and glial cells and vascular endothelial cells. Although some studies suggest that COX-1 plays a role in spinal transmission of pain, a much greater body of evidence is available supporting the concept that COX-2 is more responsible of prostaglandins involved in hyperalgesia in the peripheral and central nervous system (Samad et al., 2002). Compounds specifically blocking COX-1 fail to reduce hyperalgesia but COX-2 and mixed COX1/COX-2 inhibitors are antihyperalgesic.

NSAIDs prevent prostanoid production and sensitizing action of PGE₂ by inhibiting the COX enzyme (Vane, 1971). NSAIDs have been shown in animals to reduce hyperalgesia, reverse the inhibition of the descending opioid mediated noradrenergic pathways. There is also evidence suggesting the roles of serotonin and nitric oxide in the production of analgesia by NSAIDs (Bjorkman, 1995). They exert antipyretic effects centrally by inhibiting pyretic cytokines such as IL-1, TNF- α , and PGE₂ released from hypothalamic thermoregulatory center (Bjorkman, 1995; Botting, 2003). NSAIDs have some other central effects but their mode of action is still not known. However, some data suggest that they might interfere with prostanoid synthesis and catecholamine and serotonin turnover in the brain. NSAIDs could also mediate peripheral analgesic actions in a COX-independent way, by inhibiting dorsal root acid-sensing ion channels (ASICs) located on sensory nerve terminals (Voilley et al., 2001).

MIGRAINE AND INFLAMMATION

Migraine is associated with neurogenic inflammation in meninges characterized by CGRP and other neuropeptide release from perivascular trigeminal afferents resulting in vasodilation and plasma protein extravasation within the dura mater (Moskowitz MA, 1993). This process leads to release of inflammatory molecules such as serotonin, histamine, bradykinin and prostanoids that are all capable of further stimulating trigeminal afferent fibers to cause peripheral and central sensitization in headache (Strassman et al., 1996; Burstein R, 2001). A cocktail of those inflammatory mediators has been shown to sensitize both meningeal nociceptors peripherally and decrease the firing threshold of central trigeminal neurons in rodents. Nitric oxide (NO) is a vasoactive and pronociceptive molecule that is implicated in migraine headache (Van der Kuy, 2003). The NO donor, glyceryl trinitrate (GTN) induces delayed migraine headache and therefore GTN induced headache model is now being used for both human and animal studies (Olesen et al, 1994; Iversen, 2001). In rodents it has been shown that GTN infusion triggered iNOS expression in dural macrophages accompanied by mast cell degranulation and IL-6 expression, which led to plasma protein extravasation (Reuter et al., 2001; Reuter et al., 2002). Those inflammatory events in the dura mater are preceded by the activation of NF κ B and induction of IL-1 β

(Reuter et al., 2002). During headache attacks, pro-inflammatory cytokines are released in close proximity to trigeminal nerve fibers.

It is highly probable that the aura phase of migraine is also accompanied by pro-inflammatory molecules. During CSD, potassium ions, protons, nitric oxide, adenosine, and arachidonic acid are released into the extracellular space and under certain conditions can cause depolarization of trigeminal perivascular nerve fibers (Bolay et al, 2002). CSD has been shown to induce neurogenic inflammation in the dura mater and be a noxious stimulus that is capable of activating second order trigeminal neurons in the brainstem (Bolay et al 2002). Matrix metalloproteinase 9, which is inducible by cytokines, has been shown to be activated shortly after CSD which implies that the aura is also capable of inducing the release of inflammatory molecules (Gursoy et al. 2004). In addition, PGE2 levels are found to be elevated in the plasma during headache attacks, and migraine like symptoms can be induced by infusion of PGE2 in migraineurs (Sarchielli et al., 2000; Peatfield et al., 1981). Therefore, it is likely that inflammatory molecules and prostanoids are important mediators of migraine headache.

NSAIDs are widely used and effective drugs for both acute remedy and prophylactic treatment of migraine and tension type headache, which highlights the importance of prostanoids and their receptors in headache. Aspirin and acetaminophen are the most frequently used drugs for abortive treatment (Prior et al., 2002; Diener et al., 2006). Whether the action of NSAIDs on platelet aggregation may also account for their effectiveness in migraine prophylaxis is controversial. NSAIDs and ASA may exert more specific effects on the trigeminal and antinociceptive system in the brainstem and thalamus (Kaube et al., 1993; Jurna & Brune 1990). The selective COX-2 inhibitor rofecoxib was found to be effective in pain relief (57%) compared to placebo control (Silberstein et al., 2004), though this drug among other coxibs were withdrawn from the market due to undesired effects on cardiovascular system.

Remarkably, prednisolone infusion could be effective for status migrainous when the attack is prolonged and refractory to usual abortive medication. Glucocorticoids are also useful for management of cluster headache (Antonaci et al., 2005; Mir et al., 2003; May et al., 2006). Regarding that important mechanism of glucocorticoids is the blocking arachidonic acid release from membrane phospholipids by inhibiting phospholipase A2, those clinical applications support the notion that prostanoids are by some means involved in headache.

Despite being the most common administered group of drugs, the mode of action of NSAIDs in headache syndromes is still not fully understood and future drug developments should focus on better tolerated COX-2 inhibitors, blockade of specific prostanoid receptors such as EP₁, EP₂ and/or EP₄, inhibition of inducible mPGES-1 enzyme, or more upstream molecules such as IL-1 β .

5) NORADRENERGIC SYSTEM AND OTHER BIOGENIC AMINES

Central biogenic amine systems using norepinephrine (NE), dopamine (DA), and serotonin (5-hydroxytryptamine, 5-HT) as neurotransmitters play a significant role in headache

syndromes (D'Andrea et al., 2007; Johnson et al., 1998), besides regulating various vital functions in the cardiovascular and endocrine systems, emotional states, and energy balance (Nelson & Gehlert, 2006). Histamine, serotonin and dopamine, and norepinephrine are derived from three different amino acids respectively, histidine, tryptophan, and tyrosine. Biogenic amines exert their effects primarily through G protein-coupled receptors (Cooper et al, 2003).

β ADRENORECEPTOR BLOCKERS

Noradrenaline is the catecholamine synthesized by the action of dopamine B hydroxylase in locus coeruleus neurons that project widely throughout the CNS. The noradrenergic system has predominant innervations to all cortical layers with the highest density in the primary sensorimotor areas and limbic cortices and vascular structure in the brain (Gaspar et al., 2004). Noradrenaline mediates a diverse range of responses through α or β adrenoreceptors located both on neuronal and nonneuronal cells (Hieble, 2007). Alpha receptors are widely distributed in skin vessels, mucosa, and kidney, where their stimulation leads to vasoconstriction. Beta receptor subtypes all stimulate adenylate cyclase via Gs proteins and are abundant in the myocardium, skeletal muscle, and bronchi, where they function in myocardial excitation, broncodilation, and vasodilation (Brede et al., 2004; Owen et al., 2007; Shin & Johnson, 2007).

Non-selective β blocking drugs that have equal affinity to β1 and β2 receptors are at present the first choice preventive medication in migraine (Linde and Rossmagel, 2004; Evers et al, 2006). Propranolol is a non selective drug and pure antagonistic action without any intrinsic sympathomimetic activity on β receptors (Shanks, 1991). However metoprolol, another effective agent has greater affinity to β1 receptors. Propranolol, alprenolol, metoprolol are extremely lipophilic and easily penetrate into CNS. On the other hand, atenolol a hydrophilic drug with poor penetration into the CNS is also efficient in migraine prophylaxis (Tfelt-Hansen and Rolan, 2006). Therefore, it is still not clear which property of a β blocker drug determines the efficacy in migraine, since penetration through the blood--brain barrier (BBB), cardioselectivity, or membrane stabilizing activity are not common properties. Recent data indicates that β blockers could also be effective through central mechanisms. That is supported by Shields and Goadsby (2005) who reported that the preventive action of propranolol is partially mediated by β1 adrenoreceptor inhibition of third order trigeminovascular nociceptive neurons in the thalamus. Propranolol has also been shown to influence cortical excitability and significantly reduced the number of potassium evoked CSDs in rodent cerebral cortex (Ayata et al., 2006). Whether those effects are epiphenomenon and how they relate to CSD has to be elucidated by further investigations (Alemdar et al., 2007). It is noteworthy that Na⁺-K⁺ ATPase activity of cerebral microvessels, and the consequent transport of Na⁺ and K⁺ across the BBB, is probably modulated by noradrenergic innervations from the locus ceruleus (Harik, 1986) and by this means by β blocker agents, though its significance for headache remains indistinct.

REUPTAKE INHIBITORS OF SEROTONIN AND NORADRENALINE

Serotonergic neurons are principally located in the raphe nucleus where extensive axonal projections innervate almost all regions in the central nervous system. The action of

serotonin (5-HT) within the synaptic cleft is terminated by an active reuptake via serotonin transporter (SERT) into serotonergic neurons. Most of the serotonin is then degraded by an enzyme named monoamine oxidase (MAO) to its major metabolite, 5-hydroxyindole acetaldehyde (Cooper et al, 2003). There are at least 14 different 5-HT receptor subtypes defined in both pre and postsynaptic locations mediating diverse range of actions (Boess & Martin, 1994; Barnes & Sharp, 1999). All serotonin receptors belong to G protein-coupled receptor family except 5-HT₃ receptors which are ligand-gated ion channels (Kroeze et al., 2002). Serotonin is known to play a pivotal role in migraine pathophysiology since acute remedy medications such as triptans and ergots activate 5-HT₁ receptors particularly 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} subtypes (Beattie et al, 1994; Longmore et al., 1999). In addition, 5-HT₂ antagonisms provided by methysergide and cyproheptadine (also an antihistaminic and blocks Ca⁺⁺ channels) mediates prophylaxis in migraine headache (Mylecharane, 1991; Silberstein, 1998).

Selective serotonin reuptake inhibitors (SSRIs) potently block the active reuptake via serotonin transporter located on serotonergic neurons that leads to an increased probability of serotonin interacting with its pre –and post-synaptic receptors. SSRIs exert antinociceptive effects on via descending serotonergic fibers and primarily spinal 5-HT_{2A} or 5-HT_{2C} receptors (Honda et al., 2006). Fluoxetine-induced antinociception seems to involve central opioid pathways, since it is shown to be sensitive to blockade by naloxone and naltrexone (Singh et al., 2001). On the other hand, the efficacy of SSRIs for migraine prevention is controversial (Adly et al., 1992) and SSRIs are found to be no more efficacious than placebo in patients with migraine (Saper et al., 1994; Moja et al., 2005). SSRIs are useful in patients with chronic tension type headache though they are less efficacious than tricyclic antidepressants (Moja et al, 2005).

Serotonin noradrenaline reuptake inhibitors (SNRI) venlafaxine, duloxetine and milnacipran block both noradrenaline and serotonin reuptake and hereby have dual action mechanisms. Similar to serotonin, norepinephrine is also implicated in modulating descending inhibitory pain pathways in the central nervous system and therefore SNRIs are used for pain syndromes. Duloxetine is a selective and balanced serotonergic and noradrenergic reuptake inhibitor, and may be efficacious in the treatment of persistent and/or inflammatory pain states at doses that have modest or no effect on acute nociception or motor performance (Iyengar et al., 2004). Venlafaxine has a favorable efficacy and side effect when compared to amitriptyline and found effective for both migraine and tension type headache prophylaxis (Ozyalcin et al., 2005; Zissis et al., 2007). SNRIs seem to be more effective than SSRIs for headache and further studies with newer drugs are required to delineate their exact role in headache.

Mirtazapine, which causes reduced neuronal norepinephrine and serotonin reuptake by selectively blocking central α_2 autoreceptors and postsynaptic 5-HT₂ and 5-HT₃ receptors, has been reported to be effective in headache prevention (Bendtsen & Jensen, 2004).

Drugs such as amitriptyline, imipramine, clomipramine, desipramine, nortriptyline and maprotilene are classified as tricyclic antidepressants due to their three-ring organic chemical structure. Their mode of action is mainly through the inhibition of reuptake of

serotonin, noradrenaline, and dopamine. Tricyclic antidepressant drugs are 50- to 150-fold more potent at inhibiting transport of noradrenaline than serotonin (Cooper et al, 2003). Tricyclic antidepressants also exert their effect by blocking sodium channels (in the heart and brain), 5-HT 2A receptors, muscarinic and cholinergic receptors, histamine H1 receptors, adrenergic $\alpha 1$ receptors (Dick et al, 2007; Paudel et al, 2007). Blockade of the neurotransmitter reuptake pumps is thought to account for the therapeutic actions and the other mechanisms are thought to account for their wide range of unwanted clinical side effects. Tricyclic antidepressants bind to an allosteric site close to the neurotransmitter transporter so that the binding of and reuptake of the neurotransmitter is blocked. Amitriptyline is the only tricyclic antidepressant drug with established efficacy in migraine prophylaxis (Couch & Hassanein, 1979; Evers et al, 2006), however, their effect does not seem to depend on their antidepressant action since the usual dosage of amitriptyline is lower (up to 75 mg/day) than that used in depression and beneficial effects usually begin within the first week.

6) MODULATORS OF EXCITABILITY AND ION CHANNEL FUNCTIONS

Data acquired from various studies are consistent with the notion that general cortical dysfunction that leads to increased neuronal hyperexcitability exists in migraineurs (Welch, 2005). Whether increased excitability is relevant for other headache syndromes has not been established. Glutamate mediates excitatory neurotransmission principally through NMDA receptors that also play critical roles in the generation and propagation of CSD (Vikelis & Mitsikostas, 2007), in addition to other diverse functions such as neuronal plasticity, learning, and memory and neuronal growth (Rao & Finkbenier, 2007). NMDA receptors are cation specific ion channels that can be blocked by magnesium in a voltage-dependent manner. Glycine, polyamines, Zn^{++} , redox agents all has modulatory sites in NMDA receptors (Scatton, 1993). In the brain, magnesium has a stabilizing role on the $Na^{+}-K^{+}$ ATPase beside physiological blockade of NMDA receptors. A strategy to block excitability and/or CSD could be achieved through NR2Bs subtype inhibition (Gogas, 2006), augmenting Mg^{++} site blockade, glycine site modulators, or sigma R receptor agonism.

Presynaptic P/Q type Ca^{++} channels and voltage-gated Na^{+} channels play pivotal roles in vesicular release of neurotransmitters particularly of glutamate (Moskowitz et al., 2004). CSD is associated with increased excitability of the cerebral cortex, as shown by mutations that lead to familial hemiplegic migraine (FHM) (Moskowitz et al., 2004). In that sense mutations uncovered studying FHM are related with either vesicular glutamate release directly from presynaptic terminal (FHM1 and FHM3) (Ophoff et al 1996; Dichgans et al, 2005) or glutamate reuptake into perisynaptic astrocytes, or indirectly through effecting $Na^{+}-K^{+}$ ATPase (FHM2) DeFusco et al, 2003). The P/Q type channel is expressed throughout the brain and influences the transmission of nociceptive impulses through the trigeminal nucleus caudalis (Knight et al., 2002). Presynaptic Cav2.1 and Cav2.2 channels are implicated in excessive glutamate release in FHM1 (Qian & Noebels, 2001), which account for decreased threshold for CSD along with accompanied cerebellar symptoms. The development of new drugs that focus on the Cav2.1 and 2.2 channels provide hope for the treatment of migraine without aura.

Besides the P/Q type calcium channels, the L type calcium channel blockers (eg, verapamil) may have some role in headache prevention. They may exert their effect by potentiating opioid and acetaminophen analgesia (Weizman R, 1999). Verapamil is one of the most efficient drugs used as a preventive medication for cluster headache (May et al., 2006) though its efficacy in migraine is controversial. On the other hand, flunarizine is the most effective calcium antagonist for migraine prevention (Evers et al., 2006) and interacts likely with the release of nitric oxide from perivascular nerve fibers (Ayajiki et al., 1997). The N type calcium channel blocker (ziconotide) that is not available for oral administration has been studied for pain (Wermeling, 2005) but its efficacy for headache syndromes has to be investigated.

Tonabersat (SB-220453) is a novel benzopyran compound reported to block propagation of spreading depression and inhibit neurogenic inflammation and trigeminal ganglion stimulation-induced carotid vasodilatation (Smith et al., 2001; Parsons et al., 2000). In addition, tonabersat has been reported to attenuate trigeminal nerve-induced neurovascular reflexes in the cat (Parson et al., 2001). Particularly with the property of blocking CSD, SB-220453 has entered clinical trials in migraine. Though the preliminary results are promising with approximately 62 % decrease in headache frequency reported (Goadsby et al., 2007), further clinical studies are warranted.

The most important drugs that directly work on excitability are anti-epileptic drugs that are used as migraine preventive medications (Welch, 2005; Calabresi et al., 2007). Among antiepileptic drugs, sodium valproate and topiramate, are acclaimed. Sodium valproate is the first anti-convulsant drug that was approved by NIH for migraine prophylaxis. Sodium valproate is an effective drug for migraine prevention and has the ability to inhibit neurogenic plasma protein extravasation in dura mater (mediated by GABA_A receptors) and block the central transmission within the trigeminal nucleus caudalis (Cutrer et al., 1995). It probably blocks voltage-dependent sodium channels, T-type calcium currents, and augments the action of a GABA-synthesizing enzyme GAD (glutamic acid decarboxylase). Further studies displayed the potential of valproic acid to interfere with multiple regulatory mechanisms including histone deacetylases, GSK3 α and β , Akt, the ERK pathway, the phosphoinositol pathway, the tricarboxylic acid cycle (Kostrouchova, et al., 2007). Recently valproic acid has been shown to influence CSD generation in a dose- and time-dependent way (Ayata et al., 2006). Topiramate has the ability to suppress CSD (Ayata et al., 2006) and cortical neuronal excitability via inhibiting the AMPA/kainate glutamate receptor, potentiating the modulatory effect on the GABAergic neurotransmission (Simeone et al., 2006), influencing intracellular phosphorylation mechanisms, and blocking presynaptic voltage-gated sodium and calcium channels. It has been shown to inhibit trigeminovascular nociceptive impulses though the efficacy in models of neurogenic inflammation is yet to be determined (Storer & Goadsby, 2004). Lamotrigine, which inhibits presynaptic voltage-gated Na channels and thereby reduce glutamate release (Leach et al., 1986), is probably effective on migraine auras but did not reduce the frequency of migraine attacks (Evers et al., 2006). Gabapentin is among the third choice drugs for migraine prevention and showed a significant efficacy in one placebo-controlled trial in doses between 1200–1600 mg (Evers et al., 2006). Gabapentin basically prevents intracellular calcium entry through VGCC (voltage gated calcium channels) and are believed to modulate various glutamate transporters.

The angiotensin-converting enzyme (ACE) inhibitor, lisinopril, and angiotensin receptor type I (AT1) inhibitor, candesartan, have demonstrated efficacy in migraine prophylaxis though their mechanism of action is poorly understood (Shrader et al., 2001; Tronvik et al., 2003). Angiotensin II regulates cerebral blood flow response via AT1 receptors that inhibits GABA release in the brain (Zhu et al., 1998). AT1 receptor colocalization with glutamate and GABA receptors in the brainstem nociceptive structures implicates their modulatory role in nociception.

Specific types of K⁺ channels such as G protein activated, ATP- sensitive inward rectifier or Ca⁺⁺ activated K⁺ channels, are implicated in the antinociceptive actions of several drugs (Ocana et al, 2004; Galeotti et al., 2001). Potassium ion channels potentially modulate neuronal excitability of trigeminal neurons (Spigelman & Puil, 1989). It is noteworthy that, meclofenamic acid and diclofenac, two related molecules widely prescribed as anti-inflammatory drugs, have been demonstrated to act as novel potassium channel openers resulting in decreased neuronal excitability (Peretz et al., 2005). K⁺ channel opening may also play a role in antinociception mediated by G protein-coupled receptors in the trigeminovascular system such as GABA_B or opioid receptors (Takeda et al, 2004).

Acid sensing ion channels (ASIC) belong to ligand gated non-voltage-dependent Na⁺ channels and are activated by a decrease of pH in the extracellular milieu (Krishtal, 2003). ASIC3 is colocalized with CGRP in rat trigeminal ganglia neurons and its expression is upregulated with inflammatory mediators leading to altered firing properties of neurons (Ichikawa & Sugimoto, 2002). NSAIDs can prevent inflammation induced ASIC upregulation (Voilley et al., 2001) and activation of ASICs are modulated by protein kinase C and can be blocked by the drug amiloride.

The transient receptor potential vanilloid-1 (TRPV1) is a non selective cation channel that is activated by noxious stimuli such as capsaicin, heat or protons. TRPV1 channels are colocalized with CGRP in trigeminal neurons and probably mediate neurogenic inflammation in the dura mater in response to capsaicin (Ichikawa & Sugimoto, 2001). Since TRPV1 channels play a significant role in the generation of nociception, its antagonism could have a therapeutic potential for headache. A clinical trial with small molecule TRPV1 antagonists has been continuing in migraine patients. Activation of prejunctional adenosine A1 receptors mediate antinociception and A1 receptor agonist, GR79236, blocks CGRP release, neurogenic dural vasodilation, and reduces trigeminal nerve firing in human subjects (Goadsby et al, 2002; Honey et al., 2002; Giffin et al., 2003).

The purinergic system has two main receptors, ionotropic P2X receptor and G protein-coupled P2Y receptor family that both are activated in response to extracellular ATP (Chizh & Illes, 2001). P2X3 type purinergic receptors have become more important compared to others in regard to headache development. P2X3 receptors mediate sensitization and hyperalgesia and their effect is augmented in the presence of inflammatory mediators (North, 2003). Trigeminal nerve terminals possess high density of P2X3 receptors where CGRP potentiates their response to ATP (Ichikawa & Sugimoto, 2004). Therefore purinergic receptors are also an important target for new drug development.

7) OTHER TREATMENTS AND NEW TARGETS

BOTULINUM TOXIN TYPE A

Botulinum neurotoxin type A (BoNT) has been increasingly utilized to treat migraine, tension type headache, and other primary headache disorders. BoNT has been used clinically for the treatment of neuromuscular disorders including focal dystonias and relieve of pain associated with cervical dystonia and oromandibular dystonias. It well established that BoNT blocks the presynaptic release of the neurotransmitter acetylcholine at neuromuscular junctions by cleaving the vesicle docking protein SNAP-25, a member of the soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) proteins. However, blockage of acetylcholine release is not likely the primary mechanism by which BoNT functions as a prophylactic treatment of migraine and other headaches since reduction in pain is often noted by patients before muscle changes. Rather, the clinical benefits of BoNT may involve regulation of neuropeptide release from trigeminal ganglia neurons. Recent animal studies have provided evidence that BoNT can block the stimulated release of CGRP, glutamate, and substance P from trigeminal neurons as well as reduce c-fos gene expression in second order neurons. In addition, data from inflammatory pain models has clearly demonstrated an anti-nociceptive effect of BoNT. Taken together, it is likely that the therapeutic benefit of BoNT involves inhibition of peripheral sensitization, which results in a reduction in central sensitization and blockage of pain transmission.

OXYGEN TREATMENT OF CLUSTER HEADACHE

Inhalation of 100% oxygen, which is used therapeutically for cluster headache, has been reported to reduce the level of CGRP in blood from the external jugular vein to near normal levels. The therapeutic benefit of inhaling 100% oxygen is thought to involve vasoconstriction of cerebral blood vessels and inhibition of the trigeminovascular system. Towards this end, in recent animal studies, hyperoxia was shown to inhibit dural protein plasma extravasation caused by electrical stimulation of the rat trigeminal ganglion. Thus, the beneficial effect of oxygen treatment is thought to involve inhibition of trigeminal nerve activity that results in decreased pain transmission.

NON-INHALED INTRANASAL CO2 DELIVERY

Data from phase II clinical trials presented at scientific meetings have provided evidence that a new therapeutic approach provides relief of migraine headache (Spierings 2005). The method involves 100% carbon dioxide (CO₂), administered at a flow rate of 10 mL/second through 1 nostril while holding the breath or breathing through the mouth. The exact cellular mechanism by which CO₂ mediates these quite different physiological events is currently unknown, but is likely to occur by a mechanism different from oxygen treatment of cluster headache. Based on results from a recent in vitro animal study (Vause, Bowen et al. 2007), CO₂ treatment of cultured trigeminal ganglia neurons blocked the stimulated release of CGRP. This inhibitory effect of CO₂ on trigeminal nerve activation is thought to involve a decrease in intracellular pH and inhibition of calcium channel activity, which prevents release of neuropeptides such as CGRP. In contrast to oxygen therapy, CO₂ treatment involves noninhaled intranasal delivery and thus, would not be expected to cause a significant change in arterial CO₂ levels. However, despite the differences in delivery

methods, both CO₂ and oxygen treatments have been shown to inhibit trigeminal nerve activity. It will be of interest to determine whether CO₂ treatment can inhibit protein plasma extravasation following trigeminal nerve stimulation and whether exposure to 100% CO₂ would be effective in treating cluster headache.

GAP JUNCTION INHIBITORS

Drugs that target gap junction activity are now being tested for their ability to treat migraine. Gap junctions are protein channels that occur between cells that allows for diffusion of small molecules to pass from one cell to the other. Gap junctions are known to increase in number in neurological diseases and are thought to be involved in the initiation and propagation of cortical spreading depression as well as playing a role in peripheral sensitization of trigeminal neurons. Although its mechanism of action is not known, the compound Tonabersat is thought to inhibit gap junction communication between neurons and glia. Interestingly, communication between neurons and glia is thought to be involved in cortical spreading depression (Smith et al., 2006) as well as contributing to peripheral sensitization of trigeminal nerves within the trigeminal ganglia (Thalakoti, Patil et al. 2007). Further animal and clinical studies are needed to determine the exact mechanism of action, efficacy, and safety profile of tonabersat.

8) CONCLUSIONS AND FUTURE DIRECTIONS

Though, effective abortive and prophylactic treatments for migraine and other types of headache are available (Table 1), there is still a need for improvement since many of the currently used drugs cause unwanted side effects or are not selective for the trigeminovascular system (Table 1, 2, 3). However, a better understanding of the pathophysiology and genetic basis of migraine is directing the development of a new generation of drugs that will bind to specific cellular targets. Drugs with increased selectivity and specificity for the 5-HT_{1D} or 5-HT_{1F} receptors may replace currently available triptans. The development of oral forms of a CGRP antagonist would be very exciting.

Since inflammation plays a central role in headache syndromes, research for future studies should include inhibition of inducible mPGES-1 enzyme, prostanoid receptors implicated in headache, and the inflammatory molecules such as leukotrienes, NF- κ B, IL-1 β , and MMP9. Given the emerging evidence for CSD and hyperexcitability in headache disorders, targeting agents that reduce excitability of both cerebral cortical neurons leading to increased threshold for CSD and brainstem nociceptive neurons directly generating and transmitting pain perception will be more important clinically. Potential inhibition of CSD can be provided by targeting presynaptic P/Q type Ca⁺⁺ and SCNA1 Na⁺ channels, ionotropic glutamate receptors (iGlu5/AMPA), NR2B subunit and sigma R receptors as well as gap junction. Sensory neuron specific sodium channel (Nav1.8, Nav1.7) inhibition, K⁺ channel opening, antagonisms of purinergic P2X₃ receptors, TRPV1 receptors, ASIC3 channels, proteinase activated receptors (PAR2) are prime targets for providing antinociception.

Dopamine has gained importance and its possible therapeutic action and receptor subtypes involved other than D₂ receptor needs to be explored further (Akcali et al. 2008). Whether

disturbances in tyrosine metabolism such as dopamine and other trace amines contribute to the underlying pathology of cluster and migraine attacks needs to be investigated.

The effect of newer antiplatelet and possibly anticoagulant agents have to be tested in migraineurs, since migraine patients were shown to have an increased risk for thromboembolic events and they may have silent brain lesions in which convergence of vascular factors and the neurogenic mechanisms are largely unrevealed..

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Figure 1.

Schematic representation of prostanoid formation and peripheral sensitization. Arachidonic acid released from membrane phospholipids by phospholipases A2 is as substrate for COX-2, generating PGG2 and then PGH2. PGH2 is the substrate for most terminal prostaglandin synthases including mPGES-1 and PGIS. Inflammatory cytokines induce both COX-2 and mPGES-1 in the periphery and in the CNS. Although prostaglandins do not directly activate nociceptors, PGE₂ binds to prostaglandin E (EP) receptors, and activates phosphokinases intracellularly and increases sodium channel permeability through postreceptor events that sensitize nociceptive sensory nerve endings to other mediators (like histamine and bradykinin) and by sensitizing nociceptors to respond to non-nociceptive stimuli (allodynia). Prostanoids mediate pain sensitization through mainly EP₁, EP₂ and IP. PGE₂ and PGI₂ also indirectly potentiate TRPV1 channel and NaV1.8 sodium channel activation by phosphorylation via PKA and PKC. Those events lead to an elevation of the resting membrane potential and a reduction in the firing threshold of trigeminal nerves. In the spinal cord, PGE₂ acts on EP₂ receptors on the second order nociceptive neurons resulting in inhibition of glycine receptors through PKA-dependent phosphorylation. Glucocorticoids and NSAIDs have the ability to block phospholipase A and COX enzymes.

TABLE 1

Currently available drugs for headache treatment.

DRUGS	INDICATION	EFFICACY	DOSE (daily)	PRECAUTIONS/CONTRAINDICATIONS
ABORTIVE MEDICATION				
NSAIDs				
Paracetamol	All types of primary headache (except for cluster, SUNCT)	A	1000mg	Liver, kidney disease
Acetylsalicylic acid		A	1000mg	Bleeding disorder, peptic ulcer, gastrointestinal complications.
Ibuprofen		A	200–800mg	
Naproxen		A	500–1000mg	Caution for MOH (medication overuse headache)
TRIPTANS	Migraine attack, cluster attack (parenteral forms)			
Sumatriptan		A	6 (sc), 20(nasal), 50–100 mg (oral)	Chest discomfort, nausea, distal paresthesia, fatigue. Uncontrolled hypertension, ischemic heart / cerebrovascular / peripheral vascular disease, pregnancy, lactation, <18 Y, >65 Y.
Zolmitriptan		A	2,5–5 mg (nasal/oral)	
Naratriptan		A	2,5 mg	
Rizatriptan		A	10 mg	
Almotriptan		A	12,5 mg	
Eletriptan		A	20–40 mg	
Frovatriptan		A	2,5 mg	Caution for MOH
ERGOT ALKALOIDS	Migraine attack, cluster attack (parenteral forms)	A		Nausea, vomiting, paresthesia, ergotism. Uncontrolled hypertension, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, pregnancy, lactation, Caution for MOH
METOCLOPRAMIDE	Migraine attack	B	10–20 mg	Dyskinesia, pregnancy, childhood
OXYGEN %100	Cluster attack	A	>7 l/min (nasal)	
PREVENTIVE MEDICATION				
BETA BLOCKERS	Migraine (+hypertension)			
Propranolol		A	40–240 mg	Fatigue, insomnia, dizziness, depression, asthma, heart failure, atrioventricular block.
Metoprolol		A	50–200 mg	
ANTIEPILEPTICS	Migraine (+ epilepsy)			
Valproic acid		A	500–1800 mg	Sedation, nausea, weight gain, tremor, hair loss, liver toxicity Paresthesia, fatigue, weight loss, dysgeusia, cognitive impairment, depression
Topiramate		A	25–100 mg	
Gabapentin		C	1200–1600mg	Dizziness, drowsiness, giddiness
Lamotrigine	Migraine with aura	C	50–100 mg	Skin rash
ANTIDEPRESSANTS	Migraine, Tension type headache			
Amitriptyline		B/A	25–75 mg	Dry mouth, drowsiness, weight gain, constipation, arrhythmias, glaucoma
CALCIUM CHANNEL BLOCKERS				
Verapamil	Cluster	A	240–360 mg	Dizziness, constipation, distal edema, bradycardia, heart block

DRUGS	INDICATION	EFFICACY	DOSE (daily)	PRECAUTIONS/CONTRAINDICATIONS
Flunarizine	Migraine (childhood)	A	5–10mg	Weight gain, depression, sedation, extrapyramidal symptoms
INDOMETHACIN	Paroxysmal hemicrania, Hemicrania continua	A	150 mg	Gastrointestinal complications, peptic ulcer, nausea, purpura
PREDNISOLONE	Cluster	A	60–100 mg	Gastrointestinal symptoms, ulcer disease, diabetes, hypertension
ANGIOTENSION BLOCKADE	Migraine (+ hypertension)			
Lisinopril		C	10–20 mg	Cough, lightheadedness, blurred vision, pregnancy
Candesartan		C	16 mg	

Level of recommendation A denotes effective, B denotes probably effective, C denotes possibly effective (Evers et al, 2006; May et al, 2006; Fumal & Schoenen, 2008)

TABLE 2

Summary of mechanisms that mediate the action of currently used drugs for aborting and preventing migraine.

Abortive medications

Serotonin 5-HT 1B, D, F agonists

CGRP receptor antagonism

COX2, COX3 inhibition

Oxygen therapy (cluster headache)

Dopamine D2 receptor antagonism

Preventive medications

β adrenoreceptor antagonism

Inhibition reuptake of both NA and 5-HT

Voltage gated Na^+ , Ca^{++} channel inhibition

K^+ channel opening

GABA_A agonistic activation

AT1 receptor antagonism

5-HT2 antagonism

Carbonic anhydrase inhibition

Suppression of CSD

Increased GABA level

Inhibition of prostaglandin synthesis

TABLE 3

Therapeutics in development for treating headache disorders.

<i><u>New therapeutics</u></i>
Selective 5-HT1D or 5-HT1F agonist activity
Selective mPGE ₁ inhibition
EP ₁ , EP ₂ , EP ₄ inhibition
P/Q type presynaptic Ca ⁺⁺ modulation
Na ⁺ -K ⁺ ATPase 2 modulation
GAP junction blockade (Connexin 43)
NR2B blockade
iGLU5/AMPA inhibition
TRPV1 inhibition
ASICs blockade
iNOS inhibition
MMP9 inhibition
PAR2 antagonism
IL-1β inhibition
NFκB inhibition
CO2 treatment