Neuropeptides and Other Chemical Mediators, and the Role of Anti-inflammatory Drugs in Primary Headaches

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Abstract: Primary headaches including the migraine, cluster, and tension headaches are common neurological disorders which cause pain and disability to the patients. The pathomechanism of migraine is not very well understood however, current clinical findings indicate a possible primary brain disorder due to activation of the brain and brainstem as triggers for migraine. The headache phase of migraine may be due to activation of the peripheral nerves including the trigeminal nerve and others innervating the cranial blood vessels and release of vasoactive substances including the calcitonin gene-related peptides (CGRP), possibly leading to vasodilation and brainstem activation. Several of our studies in an experimental model of pain using electrical stimulation of the trigeminal ganglion in rats focused on various neuropeptides release from the peripheral and central trigeminal nerve terminals, however, clinically only the CGRP in migraine and CGRP and vasoactive intestinal peptide (VIP) in cluster headache were found in patient's blood. Although several drugs are used in the treatment of migraine, the non-steroid anti-inflammatory drugs (NSAIDs) and the triptan family of drugs are the first choice drugs recommended for the treatment of acute migraine headache. Although clinically very few studies detected other vasoactive/inflammatory molecules in the blood of migraine patients, sensitization of peripheral axons can involve many inflammatory mediators affecting the peripheral tissue substrates of pain. Moreover, central sensitization in the trigeminal nucleus can also contribute to additional pain responses. This article reviews neuropeptides and other molecules involved in primary headaches and major drugs proposed for their treatment in recent years.

Keywords: Neuropeptide, Headache, Anti-inflammatory drugs.

INTRODUCTION

Headache is often the manifestation of a neurological, psychological, or a systemic disease or locally derived from diseases of the eye and the ear. The intracranial pain sensitive structures include the meninges around the brain, venous sinuses of the dura mater, as well as the intracranial vessels. These structures are mainly innervated by cranial nerves V, IX, X, and the upper cervical nerves. There are also several sources of extracranial pain including the extracranial (scalp) vessels and muscles, the nasal and paranasal mucus membranes, and structures in the orbit, ear, or the oral cavity [1]. Among many causes of headache, there are three main types of primary headaches including the tension type headache, the cluster, and the migraine headaches [1, 2]. In this article we will discuss major drugs used to treat primary headaches while our focus will be more on the anti-inflammatory drugs. To elucidate the role of anti-inflammatory drugs in the treatment of primary headaches it is necessary to know the pathophysiology of primary headaches. We will also discuss the peripheral and central sensitization as a result of primary headache mechanism and their possible aggravation of the painful condition which makes the use of ant-inflammatory drugs important in controlling the pain.

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Migraine is believed to be a brain disorder that appears as attacks of often severe, throbbing head pain with sensory sensitivity to light, sound and head movements [2, 3]. It is characterized by repeated episodic headache of 4- 72 hours of duration associated by any two of (unilateral, throbbing, worsened by movement, moderate or severe) or any one of (nausea and/or vomiting, photophobia and phonophobia) features [4]. The effect of headache on person's life and the society is tremendous. A reliable data about the impact of primary headaches on the society can be drawn when counting a complete picture of the socioeconomic effect of headaches, including the effect on the life of the person, and on the possible impact even when headache-free including a fear of the next attack, as well as the effect on the partner and children [5]. Migraine is a very complex disorder and is difficult to treat. It affects about 15% of the population [6] and is one of the most costly neurological disorders. The International Classification of Headache Disorders (ICHD) adopted by the International Headache Society (IHS) in the past decades has unified the diagnostic and treatment criteria for various types of headaches [4].

There are two types of migraine headaches: 1- migraine without aura (common migraine), which comprises the majority of migraine headaches and may be accompanied by nausea, vomiting, hypersensitivity to light (photophobia), and hypersensitivity to sound (phonophobia), and may be aggravated by physical activity. 2- migraine with aura (classic migraine), which is preceded by some neurological

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symptoms which are mainly visual including the flashing lights, fortifications, scotomas, as well as sensory, and motor disturbances, collectively called aura which occur about 20-40 minutes before the headache in about 19-30% of migraine patients [7, 8]. Migraine occurs more in women, the female/male ratio is 3/1 for both types of migraine headaches [9]. Ttraditionally, five phases are described in migraine including the prodrome, aura, headache, headache termination, and the postdrome [10, 11]. The most frequently described prodrome symptoms include feeling tired and fatigue, phonophobia, and yawning [12]. From the pathophysiology point of view, three major phases including the trigger, aura, and the headache phases are important features of migraine and provide basis for its treatment. The focus on treatment of migraine should be toward a) preventive measures, and b) relieving the acute pain. Classes of medications for migraine treatment are numerous and include ergots, triptans, NSAIDs, antidepressants, anti-epilepsy drugs, antihypertensives and natural supplements [13].

Anti-inflammatory drugs have a significant role in the treatment of migraine. The European Federation of Neurological Societies (EFNS) recommends the use of oral NSAIDs and triptans for the acute treatment of migraine attacks, and for the very severe attacks, intravenous acetylsalicylic acid or subcutaneous sumatriptan (a 5-$HT_{1B/D}$ receptor agonist) are drugs of first choice. The status migrainosus can probably be treated by steroids. For the prophylaxis of migraine, β-blockers (propranolol and metoprolol), flunarizine, valproic acid, and topiramate are considered as drugs of first choice. Drugs of second choice for migraine prophylaxis are amitriptyline, naproxen, petasites, and bisoprolol [14].

PATHOPHYSIOLOGY OF HEADACHES

Migraine

Evidence in Support of Migraine Being a Brain Disorder

There are evidences that migraine is a brain disorder. Although a vascular theory was proposed triggering migraine attack [15], accumulating evidences indicate brainstem involvement in the pathophysiology of migraine [16, 17]. It seems there is a sensory dysmodulation, and a system failure of normal sensory processing of the brainstem [2] that regulates the vascular tone and the pain in migraine. Channelopathies have been linked with the aura in familial hemiplegic migraine [18, 19]. Genetic abnormalities including mutations of the P/Q type calcium channel gene [20, 21], and Na^+/K^+ pump ATP1A2 [22, 23] or sodium channel Nav1.1 mutations [24] have been linked to the pathogenesis of familial hemiplegic migraine [25-27] which are accompanied by aura. These mutations make patients more susceptible to migraine attacks [28]. Aura correspond to symptoms including mainly the visual disturbances such as flashing lights, zigzags (fortifications), scotomas, and other symptoms that may last for less than an hour before the onset of headache. Aura may follow the trigger phase in approximately 30% of migraine patients [7, 8]. Aura possibly involves cortical spreading depression (CSD), which is described as a wave of transient intense spike activity that starts in the occipital cortex and spreads rostrally with a speed of 2-6mm/min, possibly leading to a long lasting neuronal inhibition [25, 29, 30]. The CSD is followed by a characteristic regional decrease in cerebral blood flow (oligemia) in the occipital region slowly spreading anteriorly [30-33], although other theories were also proposed [34] and a recent clinical study in a small group of patients questions the theory that CSD (silent or not) is a prerequisite for migraine headaches [35]. Nevertheless, Tonabersat, a gap junction/ CSD inhibitor drug in its phase II, showed a preventive effect on attacks of migraine aura but no efficacy on non-aura attacks, in keeping with its known inhibitory effect on CSD, supporting the theory that auras are caused by CSD and that this phenomenon is not involved in attacks without aura [36].

Positron emission tomography (PET) studies suggest that the trigger phase of migraine is initiated by neuronal hyperexcitability and activation of the brain as well as the brainstem, which continues and is unaffected even after relief of the headache by sumatriptan (a potent anti-migraine drug) treatment [25, 37-39]. Migraine with or without aura is believed to be initiated by activation of the brainstem [37] the dorsal rostral pons [40, 41], the dorsal midline pons [42] or the dorsal pons [43, 44]. A dysfunction of the brainstem periaqueductal gray (PAG) matter with inhibitory effect on the nociceptive response to trigeminal stimulation [45, 46] was seen in several patients during migraine [47] and a blockade of P/Q type voltage gated calcium channels in the PAG facilitated the trigeminal nociception [48]. The PET studies show a higher regional cerebral blood flow (rCBF) in the contralateral brainstem [37] and dorsal pons [40] in migraine patients without aura during an attack compared with the headache-free state, and that the brainstem [37, 42] and hypothalamus [42] activation persisted even after headache relief by sumatriptan (an anti-migraine drug).

Molecular Mechanisms Involved in the Headache Phase of Migraine

Migraine attack is usually followed by headache located mostly in the frontotemporal region. The cranial pain sensitive structures such as the blood vessels, the cerebral sinuses, meninges and their innervations as well as their neurotransmitters including their neuropeptide contents and receptors are involved in the generation and conduction of pain, while the parenchyma of the brain itself is insensitive to pain. The headache phase of migraine is associated with the release of neuropeptides including the CGRP and inflammatory mediators in the peripheral tissue causing dilation of the blood vessels while release of neurotransmitters/ neuromodulators in the brainstem and spinal cord activates the pain processing network in the headache phase of migraine [1, 15, 38, 49-51], although some studies indicate that migraine pain started without initial dilatation of the middle cerebral artery [52], see below. Perhaps one of the main roles of the anti-inflammatory drugs would be to interfere with the molecular mechanisms involved in the headache phase of migraine.

The trigeminovascular theory of Moskowitz proposes that a trigger for headache (such as injury to the blood vessel wall) is accompanied by local production and synthesis or transport of molecules (e.g., serotonin, histamine, bradykinin, prostaglandins) from circulation which are nociceptive (induce pain) which stimulate sensory nerve fibers to release neurotransmitters (including the substance P) locally from

axonal varicosities leading to antidromic conduction [depolarization-induced substance P (SP) release into the blood vessel wall] and orthodromic conduction (convey the information to the brainstem and higher brain centers to register the pain). This leads to vasodilation and build up of vasoactive substances leading to a local inflammation and headache [15]. This inflammation is mediated by neural activity and is therefore referred to as "neurogenic inflammation". Over years the growing evidence indicates that the trigger for migraine may not be the trigeminovascular theory, rather it might be primarily in the brainstem and the brain [2, 25] however, many agree that the trigeminal nerve and its innervation of the cranial vessels are involved in the pain phase of migraine.

Pathophysiology and Molecular Alterations in Tension Type Headache

Tension-type headache (TTH) is characterized by a diffuse and dull, band-like headache associated with tension which may become worse on touching the scalp and become aggravated by noise. TTH is the most common form of the primary headaches and has two forms: chronic and episodic, which commonly co-exist with depression. The pain is characterized by being daily or frequent, last for many hours to days, may get worse towards the end of the day and may persist over many years [53, 54]. The mechanism of pain is believed to be muscular. There is also an increased tenderness of the peripheral (pericranial) myofacial tissue and an increased excitability of peripheral muscle afferents in TTH [55], as well as an abnormal pain processing in the central nervous system [56, 57], contributing to the "central sensitization". The referred pain from trigger points (primary hyperalgesic zones) in the head, and posterior cervical, as well as shoulder muscles might be responsible for the development of central sensitization in chronic TTH headache [58].

Neuropeptides (such as CRRP) levels in the CSF of tension headache patients [59] is not changed. Blood withdrawn from peripheral (antecubital veins) or cranial (jugular vein) circulation of chronic TTH patients reveal normal plasma levels of CGRP, vasoactive intestinal peptide (VIP), SP, and neuropeptide Y (NPY) [60, 61]. Consistent with this, infusion of the nitroglycerine in chronic tension headache patients did not change the plasma CGRP levels during and after the experiment [62], but interictal plasma CGRP level was increased in eight patients with a pulsating pain quality and suggests that headaches with symptoms that fulfill International Headache Society criteria for TTH may be pathophysiologically related to migraine, if the headache has a pulsating quality [61]. If CGRP involvement in TTH is proven, then drugs inhibiting the release of CGRP or blocking its receptor may play a role in the treatment of TTH.

Pathophysiology and Molecular Alterations in Cluster Headaches

Cluster headache (CH) is characterized by a severe unilateral pain around one eye, which is associated with conjunctival injection, lacrimation, or rhinorrhea, and may occasionally be associated with a transient Horner's syndrome resulting in characteristic loco-regional signs and symptoms of facial parasympathetic involvement [63, 64]. The pain may last for 10-120 minutes, with a frequency of once or many times per day and can often waken the patient from sleep at night. Clusters of attacks are separated by weeks or even months [54]. Cluster headache is the most frequent trigeminal autonomic cephalalgia (TAC) and the circadian rhythmicity nature of its attacks together with the neuroendocrine abnormalities, suggest a neurochronobiological disorder with a central-diencephalic pathogenetic involvement. Functional neuroimaging studies reveal the activation of posterior hypothalamus during cluster attack [65-67], the paroxysmal hemicrania (PH) [68], as well as the short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) [69]. Paroxysmal hemicrania is a severe unilateral headache that lasts 2 to 30 minutes, occurs more than five times daily, and is associated with trigeminal autonomic symptoms, which is responsive to indomethacin. The CH, PH, and SUNCT have been grouped as the trigeminal autonomic cephalalgia (TACs) in the second edition of International Headache Society (IHS) classification [4].

Neuropeptides have also been implicated in the pathogenesis of CH. Plasma level of neuropeptides is altered in CH patients. The CGRP and VIP (a parasympathetic neurotransmitter) levels increase in the cranial venous blood in patients with episodic CH, while the NPY and SP levels do not change [70]. Both, oxygen treatment or subcutaneous injection of sumatriptan aborted the pain and normalized the CGRP levels. Nitroglycerine-induced CH also led to an increased CGRP build up in extracerebral circulation [71]. The increased CGRP and VIP levels is believed to be due to activation of a brainstem reflex, with trigeminal nerve being the afferent limb and cranial parasympathetic outflow component of the facial nerve (CNVII) serves as the efferent limb [72-75]. The pathophysiology of CPH may resemble that of cluster headache due to activation of both sensory and parasympathetic cranial fibers [75]. Samsam and coworkers recently reviewed the neuroanatomical and neurochemical substrates of primary headaches [76].

TREATMENT OF PRIMARY HEADACHES

Serotonin Receptor Agonistic Drugs

Serotonin (5-HT) has long been implicated in the pathogenesis of migraine. Serotonin is a monoamine neurotransmitter synthesized in serotonergic neurons in the CNS and is a vasoconstrictor which controls the cerebral blood flow [77], that plays a significant role in the pathophysiology of migraine [15, 78], stroke, and vasospasm. Pial arteries and arterioles of the rat are innervated by central serotonergic fibers with a possible origin from both median and dorsal raphé nuclei [78]. Brain 5-HT synthesis is highest during migraine attacks, lowest after sumatriptan, and intermediate when patients are migraine free. In migraine patients, there is a low cortical serotonergic tone interictally, but a widespread increase in brain serotonin synthetic rate during attacks, and that triptans exert a negative feedback regulation of brain 5-HT synthesis concurrently with modulation of pain pathways [79]. A low central 5-HT disposition [80] associated with an increase in 5-HT release during attack seems to be the change of 5-HT metabolism proposed in migraine [81]. Serotonin, prostaglandin (PG)-I_2, and histamine content of the

mast cells promote a robust sensitization and activation of meningeal nociceptors, while PGD_2 and leukotriene C_4 are largely ineffective [82]. The 5-HT_{1B} receptor is largely found on the cranial blood vessels. The 5-HT_{1D} receptor is prejunctionally found on peripheral trigeminal nerve terminals (e.g.: in the meninges), and the 5-$HT_{1B/D/F}$ receptors are found on the central trigeminal neurons in the brain stem [25, 83-85]. Sumatriptan [83, 86] as well as the other triptan family of drugs have agonistic activity on serotonin (5-$HT_{1B/D}$) receptors and are currently being used to treat migraine, see [87] for review.

Treatment of the acute migraine attack can be divided to the prodromal phase, and the headache phase. During the prodromal phase the triptan family of drugs including sumatriptan, rizatriptan, naratriptan, almotriptan, eletriptan, and zolmitriptan are used which can effectively and rapidly abort or significantly reduce the severity of migraine headaches in many patients. Oral administration of triptans is preferred by patients however, it may not relieve the pain completely due to inhibition of gastrointestinal motility and a delayed gastric emptying [88, 89]. The non-oral formulations (subcutaneous, nasal spray and suppositories) act faster.

The triptan family drugs [90-94] especially the subcutaneous injectable form of the sumatriptan constrict the coronary arteries as well, and can cause side effects such as chest pain and tightness and severe symptoms in people with coronary/ cardiovascular diseases. Other adverse effects of triptans include the throat tightness, fatigue, dizziness, paresthesia and myalgia, as well as the serotonin syndrome [87]. Triptans induce migraine progression in those with high frequency of migraine at baseline (10-14 days per month), but not overall [95]. Comprehensive studies on the use of various triptans and others, their effects and side effects can be found else where, please see [96-98] for review.

Dihydroergotamine (DHE) is a derivative of ergotamine which is a vasoconstrictor and another drug that is most effective when given during the prodromal phase of migraine. It is an older anti-migraine drug acting on 5-$HT_{1B/D}$ receptors as well as other serotonin, dopaminergic and adrenergic receptors responsible for the adverse effects of the drug including the nausea and vomiting, muscle cramps, difficulty swallowing, chest discomfort, tingling sensation in the extremities, nasal congestion, depression, fatigue and vascular effects [97, 99]. It is contraindicated in pregnancy, and in patients with coronary artery disease, or peripheral vascular disease. DHE is associated with a markedly lower incidence of medication-withdrawal headache, nausea, and vomiting than is ergotamine tartrate [100]. In general, the use of more specific drugs, the triptans, causing less adverse events and being more effective, is preferable to the use of the ergotamine in the acute treatment of migraine [101]. Oral triptans outperform oral ergotamine most because of the extremely low (< 1%) oral bioavailability of ergotamine [102].

CGRP Antagonist Drugs in the Treatment of Migraine

There are strong evidences for the CGRP involvement in migraine. In *vivo* electrical stimulation of the rat trigeminal ganglion (TG) among several other animal models [103] is used as an experimental method to mimic migraine like attacks. Electrical stimulation of the rat TG leads to extravasation of plasma proteins from the postcapillary venules in the areas innervated by the trigeminal nerve (e.g.: dura), which is thought to be mediated by the release of neurotransmitters/ neuromodulator including the neuropeptides [104]. This mimics some of the characteristics of inflammation and pain. A unilateral electrical stimulation (5 Hz, 5ms, 0.1- 1 mA, for 5-30 min) of the TG [105] or of the dural surface [106] with similar parameters (10-20 V, 5-10 Hz, 10-30 min) in deeply anesthetized rats to mimic a vascular type headache leads to an increased CGRP-immunoreactivity and significant swelling and enlargement of the ipsilateral perivascular nerve terminals in the dura mater [105] which then disintegrate or burst as stimulation continues leading to the release of their neuropeptide content into the blood vessels or into the tissue causing vasodilation and increasing the meningeal blood flow [106] as well as a possible inflammatory response in the tissue. CGRP is a vasodilator [107] and the nitrovasodilators were seen to activate sensory fibers to release CGRP, which in turn relaxes cerebral vascular smooth muscle by activating guanylate cyclase [108]. Increased CGRP levels in the superior sagittal sinus of the rat following electrical stimulation of the TG was attenuated when the rats [109] or cats [110] were treated with dihydroergotamine and/or sumatriptan or by topical application of the CGRP antagonist hCGRP8-37 [106] prior to electrical stimulation.

Sumatriptan (i.v.) given prior to electrical stimulation of the TG, prevents disintegration of the axon terminals and release of CGRP in the rat dura mater [111] presumably by an agonistic action at 5-HT_{1D} receptors in nerve terminals. Subcutaneous administration of sumatriptan, normalizes the elevated CGRP levels and relieves the headache [110] of migraine patients. Moreover, CGRP [112, 113] stimulate mast cell degranulation and release of inflammatory mediators including histamine from meningeal mast cells. Histamine produces direct vasodilatation and activates a subset of largely non-mechanically sensitive, non-CGRP containing afferents in the rat meninges [113] which may contribute to the peripheral sensitization and aggravation of headache. Nevertheless, there are evidences that migraine pain may already start during cerebral hypoperfusion [52, 114-116], and that migraine pain started without initial dilatation of the middle cerebral artery [52].

Examining the central transmission of pain, several experiments reveal that electrical stimulation of the TG releases CGRP [117, 118] and SP as well as NKA [118-120] from the central terminals in the ipsilateral caudal trigeminal nucleus (CTN) as well as some patchy release (depletion) of CGRP, SP and NKA from the contralateral CTN [121]; this latter may explain some bilateral headaches in one third of migraine patients. Depletion of neuropeptides is significant in CTN in the lower medulla where majority of the central terminals of the dull pain conveying afferents of the TG neurons terminate. Release of neurotransmitters including neuropeptides in the CTN activates the neuronal network and increases the expression of the early gene, the c-fos oncoprotein in the CTN [111].

A possible co-transmittory or co-modulatory role of these neuropeptides in transmission of pain in the trigeminal system has also been suggested [120] through CGRP being able to enhance the action of SP when these peptides are co-

administered in the CNS [122, 123] by possibly inhibiting an enzyme involved in SP degradation [124, 125], and/ or potentiating the release of substance P from the primary afferent terminal to promote the transmission of nociceptive information induced by mechanical noxious stimuli [126].

Glutamate, a major excitatory neurotransmitter which is released from the trigeminal central terminals is also involved in the activation of the central neurons in the trigeminal pain processing pathway. Glutamate has been implicated in cortical spreading depression, trigeminovascular activation and central sensitization [127-129]. Consistent with these, Memantine and MK-801, selective NMDA receptor antagonists partially reduced capsaicin induced c-fos expression [130]. At the moment, CGRP is the main neuropeptide that seems to play a significant role in headache, although more research is necessary [131]. It is very likely that CGRP release from peripheral trigeminal nerve terminals mediates dilation (directly and indirectly) of the intracranial and extracranial blood vessels and its central release activates the trigeminal pain processing neuronal network in the brainstem. Because of the several side effects of the triptans, drugs with non-vasoconstrictive and non-serotoninergic properties such as BIBN4096BS blocking the CGRP receptor were proved to be effective in the treatment of migraine headache and prevent the CGRP-mediated vasodilation or activation of trigeminovascular afferents [132]. The structure of the CGRP receptor is unusual since it is comprised of a hetero-oligomeric complex between the calcitonin receptor-like receptor (CRL) and an accessory protein called receptor activity-modifying protein 1 (RAMP1) required to transport CRL to the plasma membrane. Both the CLR and RAMP1 components have extracellular domains which interact with each other and together form part of the peptide-binding site [133]. The RAMP1 is functionally rate limiting for CGRP receptor activity in the trigeminal ganglion [134]. The CRL can function as either a CGRP receptor or an adrenomedullin receptor, depending on which members of RAMPs, are expressed. RAMP1 presents the receptor at the cell surface as a mature glycoprotein and a CGRP receptor. RAMP2-transported receptors are core-glycosylated and are adrenomedullin receptors [135, 136]. The CGRP were divided into CGRP1 and CGRP2 receptors [137]. The CRL and RAMP1 was considered CGRP1 receptor while it is now apparent that the CGRP(2) receptor phenotype is the result of CGRP acting at receptors for amylin and adrenomedullin. Accordingly, the term "CGRP(2)" receptor was recommended not to be used any longer and instead, the "CGRP(1)" receptor should be known as the "CGRP" receptor [138]. Several signaling molecules and second messengers such as cAMP or cGMP, and the ATP-sensitive K^+ channels and the large-conductance Ca^{+2}-activated K^+ channels [139-142] or extracellular calcium and T-type calcium channels have been implicated in CGRP receptor activation [143]. The CGRP receptor antagonist BIBN4096BS is a viable anti-migraine drug, examined on human arteries [144, 145] and laboratory animals [146-148] by blocking the responses evoked by alpha-CGRP and capsaicin, or electrical stimulation [149], and reduces the neurogenic increases in dural blood flow without changing basal vascular parameters [150, 151], whereas sumatriptan attenuated only vasodilation induced by electrical stimulation [149].

In the clinical trials the drug did not constrict coronary arteries [144, 152, 153], which shows an advantage over the triptan family drugs.

Therefore, an antagonistic action of the drug on both peripheral (on target tissues) and central CGRP receptors in the trigeminal nucleus makes these drugs potential candidates for treatment of migraine, especially in patients with cardiovascular disease, where triptans use might be limited due to their vasoconstrictive activity on $5\text{-}HT_{1B/D}$ receptors on coronary arteries, or in patients with second rebound attack, see [11, 103] for review.

The novel, orally administered calcitonin gene-related peptide (CGRP) receptor antagonist, MK-0974 (telcagepant), is an effective drug and generally well tolerated for the acute treatment of migraine [154]. Telcagepant 300 mg is effective in relieving pain and other migraine symptoms at 2 hours and provides sustained pain freedom up to 24 hours. In this study, telcagepant 150 mg was also effective. Telcagepant was generally well tolerated [155]. Pre-treatment with olcegepant (BIBN4096BS, 900 μg/kg) inhibited the capsaicin-induced expression of “fos” throughout the spinal trigeminal nucleus in anesthetized rats by 57%, suggesting that CGRP receptor inhibition is likely to occur in the central nervous system rather than in the periphery including the trigeminal ganglion [156].

Although both olcegepant (BIBN4096BS, given intravenously) and telcagepant (MK-0974, given orally) have been shown to be safe and well tolerated [157, for BIBN4096BS], as effective acute anti-migraine agents in phase I, phase II, and for telcagepant phase III studies [158], recent data reported elevated transaminase levels when telcagepant was dosed daily rather than acutely. It was concluded that, if these hepatic toxicities are not observed in ongoing/future trials of the acute use of telcagepant, then this agent may offer an alternative to triptan therapy for the treatment of migraine [159]. Therefore, the potential for a specific acute antimigraine drug, without producing vasoconstriction or vascular side effects and with an efficacy comparable to triptans, is enormous [85].

CGRP is also released within the trigeminal ganglia suggesting possible local effects on satellite cells, a specialized type of glia that ensheath trigeminal neurons which may contribute to peripheral sensitization [160, 161].

Comprehensive reviews on the function of CGRP in migraine, and the use of CGRP-receptor antagonists as a novel approach in the treatment of migraine attack are available [85, 162].

Blocking Nitric Oxide Synthesis and/or Receptor in Treatment of Headache

Nitric oxide (NO) is a strong vasodilator that regulates the arterial diameters as well as the cerebral and extra cerebral cranial blood flow and therefore, is involved in nociceptive processing and migraine [163, 164]. The TG neurons also express nitric oxide synthase (NOS) [163, 165]. Intravenous (i.v.) infusion of nitroglycerine [166] and hα-CGRP [167] in migraineurs can produce a migraine-like effect. Nitric oxide is also involved in the electrically evoked flow increases mediated by CGRP released from dural afferent

fibers. Such cooperation and synergistic effect of NO and CGRP on the stimulated blood flow was postulated to be in part due to a NO mediated facilitation of the CGRP release [168], while prostaglandins are not significantly involved [169]. It seems that CGRP synthesis and release within the trigeminal ganglion neurons are coordinately stimulated by NO. Consistent with this, NOS inhibitors antagonized neurogenic and CGRP induced dilation of dural meningeal vessels [170]. Moreover, CGRP receptor activation of the cultured trigeminal ganglion neurons increases endogenous CGRP mRNA levels and promoter activity (134). There are different reports about the NO-dependent cyclic guanosine monophosphate (cGMP) signaling, or the CGRP-dependent cyclic adenosine monophosphate (cAMP) involvement in headache and migraine [142], or the NO action requiring extracellular calcium through T-type calcium channels [143]. Sumatriptan greatly represses NO stimulation of CGRP promoter activity and secretion [143]. Inhibition of the NO production, or blockade of steps in the NO-cGMP pathway, or scavenging of NO have been proposed in treatment of migraine and other headaches [171]. However a recent study in 10 healthy subjects using glyceryl trinitrate (GTN) to induce headache, led to a peak headache intensity of 4 (range 2-6) in 0-10 scale, while jugular vein CGRP, VIP, NPY, or somatostatin (SST) levels were unchanged indicating the NO donor GTN appears not to induce headache via immediate CGRP release [172].

Mitogen-activated protein kinase (MAPK) which respond to extracellular stimuli including the proinflammatory cytokines are involved in CGRP regulation of inducible NOS (iNOS) expression and NO release in glial cells. CGRP activates the MAPK reporter genes, Elk, ATF-2, and CHOP in cultured TG glial cells, as well as increases the nuclear staining for the active forms of the MAPKs including extracellular signal-regulated kinase (ERK), c-Jun amino-terminal kinase (JNK), and p38. In addition, over-expression of MAPK kinases increased iNOS expression and NO production in glial cells indicating the CGRP receptor activation stimulates iNOS gene expression via activation of MAPK pathways in trigeminal ganglion glial cells [173]. This may have an important role in peripheral sensitization that is discussed below. Although GW274150, a novel and highly selective inhibitor of the iNOS in the peripheral tissues, shows analgesic effects in rat models of inflammatory and neuropathic pain [174], it is not clear if it can prevent migraine in clinical trials [175].

Neurokinin, and Other Neuropeptides Receptors Blockade in Treatment of Headache

In spite of a few studies reporting the increased plasma SP level [176], or NKA increase in the blood of migraine patients [177], many clinical studies failed to find SP in the blood of migraine sufferers [25, 177-179] during headache. Moreover, the SP receptor (neurokinin-1) antagonists failed to alleviate the pain of migraine patients [180-182]. Although this may indicate involvement of neurogenic vasodilatation mediated by CGRP via the direct (i.e., endothelium-independent) relaxation of the vascular smooth muscle is the dominant mechanism rather than the inflammation and plasma protein extravasation mediated by SP in human meningeal vessels during migraine [183], the peripheral sensitization is an important phenomenon which should be considered here aggravating the headache process through inflammatory mediators sensitizing the nociceptors.

Peripheral sensitization is discussed in more details in this article (see below please).

Several neurotransmitters/ neuromodulators exist in the primary sensory neurons of the TG, the central axons of which terminate in the brainstem trigeminal nuclei. The TG cells include numerous glutamate-, SP-, NKA-, CGRP-, cholecystokinin (CCK-), somatostatin (SST-), VIP-, NPY-, peptide 19-, and galanin (Gal)-IR small and medium size neurons and many NOS- and parvalbumin (PV)-IR neurons of all sizes as well as fewer, mostly large, calbindin D-28k (CB)-IR neurons. Most of the large ganglion cells are surrounded by SP-, CGRP-, SST-, CCK-, VIP-, NOS- and 5-HT-IR perisomatic networks [165, 184]. The interaction between the central neurons as well as the central sensitization is discussed below, in this article.

Somatostatin (SST) is also involved in the modulation of nociceptive information in the spinal trigeminal nucleus and spinal cord of the rat and also regulates the hypothalamic metabolic, neuroendocrine and autonomic functions [185]. Somatostatin [186] and opiates inhibit the release of SP from sensory neurons and relieve pain and autonomic symptoms of cluster headache [187, 188] and migraine attacks [189]. Intravenous administration of SMS 201-995 (a synthetic octapeptide analogue of somatostatin), blocked plasma protein (125I-albumin) extravasation within rat and/or guinea pig dura mater following unilateral electrical stimulation of TG or capsaicin administration [190], indicating that octreotide action targets the peripheral tissues to relief pain. Moreover, electrical stimulation of the TG leads to a depletion (and release) of SST in the ipsilateral CTN [191]. Please see Samsam *et al.* [192] for a quick review of the neuropeptides involved in headache.

Octreotide failed to suppress C-fos-IR of rat CTN or pain behaviours following intracisternal capsaicin administration [193], which might possibly be due to its poor penetration to the brain [194, 195], but may also indicate the involvement of other neurotransmitters/ neuromodulators in the activation of the trigeminal nucleus. The SST-antagonist "cyclo-somatostatin" injection into the posterior hypothalamus of the rat decreased the A- and C-fiber responses to dural stimulation, leading to decreased spontaneous activity probably mediated via GABAergic mechanisms [196].

Somatostatin analogues may be highly effective in aborting headache associated with functionally active pituitary lesions, particularly in the case of acromegaly, presumably by inhibition of nociceptive peptides [197].

Somatostatin receptors especially the SST2A subtype are present on most meningiomas and are over-expressed in recurrent meningiomas. Administration of long-acting somatostatin/ sustained-release-SST (Sandostatin LAR) in a small number clinical trial proved to offer a novel, relatively non-toxic alternative treatment for recurrent meningiomas [198]. The triptans transduce "G" proteins at 5-HT $_{1B/D}$, therefore, investigating agonists at other G(i) protein-coupled receptor types appropriately located (e.g., SST or adenosine A) may lead to new anti-migraine drugs [199].

Opiates Role in Relieving the Headache

Opiates are able to decrease the duration of the action potential of the nociceptors by decreasing the Ca^{++} influx into the neuron, which leads to a decrease in neurotransmitter release from primary afferents. This effect is on the presynaptic compartment. In addition, opiates can hyperpolarize the postsynaptic neurons in the dorsal horn by activating the K^+ conductance outward, decreasing the intracellular positive charges [200].

A descending antinociceptive pathway originating in the midbrain periaqueductal gray (PAG) mater [201-204] sends serotonergic excitatory projections from the midline of the nucleus raphe magnus and other serotonergic nuclei to the neurons of medulla and spinal cord to facilitate antinociception by activating the opioidergic interneurons to release opiates via direct and indirect (through enkephalinergic interneurons) connections.

In addition, opiate (such as dynorphin B) containing nerve fibers surround the brain blood vessels [205]. Endomorphins such as endomorphin-2 is also found in primary sensory afferent fibers, which might serve as endogenous ligands for pre and post synaptic mu-receptors to modulate pain perception [206]. Met-Enk is present in primary afferent fibers and TG [207-209] as well as in the neurons/ terminals in several brain regions including the mesencephalon and spinal cord, and Met-Enk may be released from such terminals upon somatic stimulation [191, 210]. Increased levels of Met-Enk [211, 212] and β- endorphin levels are reported in the plasma of migraine patients; see Edvinsson L., [75] for review.

Opioids block the nociceptive neurotransmission within the brainstem trigeminal nuclei, and inhibit neurogenic dural vasodilation via an action on mu-opioid receptors located on trigeminal peripheral fibers innervating dural blood vessels [213]. The endogenous opiate containing neurons in the spinal cord and the brain stem are the local- circuit Enk-ergic interneurons in the superficial dorsal horn of the spinal cord which are activated by such brainstem serotoninergic and noradrenergic neurons, inhibit the presynaptic release of neurotransmitters from primary sensory central terminals as well as inhibit the postsynaptic neurons [200].

There are several concerns with the opioid analgesic use in treatment of migraine; these include the overuse and abuse, leading to medication overuse-headache as well as the tolerance [214, 215]. Clinical studies in patients with medication overuse headache, reveals a lower rate for patients overusing triptans than analgesics [216]. The management of medication overuse should aim for patient education, biobehavioral therapy, withdrawal of overused acute medications, bridge therapy for withdrawal headache, initiation of preventive medication, and close follow-up [217]. Moreover, clinical experiences indicate a general inefficacy of opioids in the management of chronic daily headache [218], and a recent clinical investigation reported that pain relief in migraine patients was not related to the use of opioids vs. non-opioids [219].

The non-steroid anti-inflammatory drugs (NSAIDs) including aspirin, naproxen and meclofenamate are used during the headache phase and depending on the severity of the pain, other pain killers such as opioids, codeine sulphate or meperidine might be necessary to treat the pain [220].

A large population-based longitudinal study to assess the role of specific classes of acute medications in the development of transformed migraine in episodic migraine sufferers indicates that individuals who used medications containing barbiturates or opiates were at increased risk of transformed migraine [221].

Peripheral Sensitization

Although the vascular dilation as a trigger for migraine is not widely accepted, rather the receptor site activation is believed to be more important in migraine [3], the peripheral and central sensitization are complications of the pain processing network that may aggravate the headache and implicates other considerations as well. Chemical stimulation of the peripheral axons of the TG primary neurons in the cerebral dura by inflammatory mediators increases neuronal activity in rat trigeminal ganglion (TG) and enhances their mechanical sensitivity, such that they are strongly activated by mechanical stimuli that initially evoke little or no response. Such chemosensitivity and sensitization of the meningeal afferents is believed to be responsible for the intracranial mechanical hypersensitivity and contribute to the throbbing pain of migraine [222].

Peripheral sensitization occurs when peripheral axons are soaked with the "inflammatory" soup including the prostaglandin E2, bradykinin, serotonin and cytokines along the vasculature of the cerebral dura mater, sensitizing the nociceptors to become hyperresponsive to the otherwise innocuous and unperceived rhythmic fluctuation in intracranial pressure produced by normal arterial pulsation [223, 224]. Inflammation leads to the production of a soup of cytokines, growth factors and inflammatory mediators including H^+, K^+, serotonin, bradykinin, histamine, ATP, PGE_2, interleukin-1 (IL-1), tumor necrosis factor-alpha (TNFα), and nerve growth factor [127]. Various ligand-gated ion channels and G protein-coupled receptors are found on the peripheral nerve terminals where the inflammatory mediators bind to them directly. Some of these e.g.: H^+, ATP and serotonin directly activate the nociceptors by interacting with ligand-gated ion channels on the nerve terminals. Some such as Vanilloid receptor (VR1) and the epithelial sodium channel degenerins, are acid-sensing ion channels (ASICs) that react to the high level of acidity in the inflamed tissues; other inflammatory mediators do not directly activate the nerve terminals, but are able to sensitize them by reducing the transduction threshold which involves phosphorylation of the tetrodotoxin (TTX)-resistant sodium channels (TTXr) driven by various inflammatory mediators including the PGE_2 and 5-HT actions on their receptors, and activation of the intracellular signalling molecules such as protein kinase -C and -A (PKC) and (PKA). This reduces the transduction threshold of the terminals known as peripheral sensitization [127].

An exaggerated intracranial mechanosensitivity such as worsening of headache by coughing, or physical activity can be seen in headache including the migraine which is thought to be due to a sensitization of meningeal afferents to mechanical stimuli [222]. Irritation of the cerebral dura mater with chemicals can activate and sensitize the primary affer-

ent neurons as well as the central trigeminal neurons. Chemical sensitization of meningeal nociceptors also leads to central sensitization of second-order trigeminovascular neurons that receive convergent input from the dura and skin to extracranial mechanical and thermal stimulation which mediates cephalic allodynia (the scalp and muscle tenderness) that develops during migraine [223].

Using single-unit recording in an animal model of intracranial pain, the ability of sumatriptan to prevent and/or suppress the peripheral and central sensitization was tested. In both the peripheral and central neurons, the drug failed to attenuate the increased spontaneous activity established during sensitization [225]. They suggested that neither peripheral nor central trigeminovascular neurons are directly inhibited by sumatriptan and that the analgesic action of triptan could not be attained in the presence of central sensitization. Triptan action was therefore proposed to be exerted through blockade of the synaptic transmission between the two types of neurons [225, 226] in the trigeminal nucleus, see below.

The ongoing activity of single wide-dynamic range (WDR) central neurons recorded with microelectrodes in the subnuclei of the spinal trigeminal nucleus indicates that the processes of sensitization, is driven remotely by ongoing afferent input from the periphery [227]. It is possible that in addition to CGRP other inflammatory mediators including those in the mast cells stimulate the nociceptors in the cerebral dura leading to aggravation of pain by peripheral sensitization. Indeed neuropeptides such as CGRP, hemokinin A, pituitary adenylate cyclase activating peptide (PACAP), and SP can activate mast cells leading to secretion of vasoactive, pro-inflammatory, and neurosensitizing mediators; thereby contributing to migraine pathogenesis, see [15, 228] for review.

Peripheral sensitization is inhibited by the NSAID "naproxen", a non-selective cyclooxygenase (COX) inhibitor or selective COX-2 inhibitor (NS-398), suggesting that local COX activity in the dura could mediate the peripheral sensitization that underlies migraine headache [197]. The potent COX inhibitor S(+)-flurbiprofen (10^{-6} M) strongly reduced the basal and stimulated iCGRP release and abolished $iPGE_2$ release while the $5\text{-}HT_{1B/D}$ agonists were ineffective [229].

Other drugs such as beta-blockers used in the treatment of migraine may partially owe their action by inhibiting the release of inflammatory mediators. Basal release of PGE_2 is enhanced by norepinephrine [230] and this enhancement was reduced by serotonin through $5\text{-}HT_{1D}$ receptors, indicating that sympathetic transmitters may control nociceptor sensitivity via increased basal PGE_2 levels, a possible mechanism to facilitate the headache. VIP is also involved in NO modulation. Cervical sympathectomy induced a significant increase in dura mater NO levels, while VIP decreased NO to control levels and increased the norepinephrine vessel-contraction responses of sympathectomized rats [231].

Interactions between the glial and neuronal cells in the sensory ganglia are also believed to be involved in peripheral sensitization. The various effects of glial factors on neuronal activation and peripheral sensitization which are being described in recent years are in favor of using anti-inflammatory drugs in the treatment of headache and open several new targets in migraine therapy. In an effort to test possible modulatory effects of glial factors on trigeminal neuronal activity, stimulation of the cultured satellite glial cells (SGCs) by two pro-inflammatory mediators, the interleukin-1 (IL-1)-β and the NO donor diethylenetriamine/nitric oxide (DETA/NO) elevated PGE_2 release by satellite cells. The stimulatory effect of IL-1β was mediated mainly by up regulation of the inducible form of COX2 enzyme, while NO increased the constitutive COX activity [161]. Conditioned medium taken from such satellite cells cultures activated by either IL-1β or NO increases the evoked release of CGRP by trigeminal neurons. It has been postulated that satellite cells may contribute to migraine-related neurochemical events by autocrine/ paracrine stimulus (such as IL-1β and NO), activating the CGRP release and the potential for a positive feedback loop to aggravate migraine [161]. In addition the glial iNOS and NO release are also regulated by activation of CGRP receptor and it was proposed that following trigeminal nerve activation, CGRP secretion from neuronal cell bodies activates satellite glial cells that release NO and initiate inflammatory events in the ganglia that contribute to peripheral sensitization in migraine [160]. Another study proposes the iNOS to have an effect in the peripheral tissues (since it was not detected in the dorsal root ganglia, spinal cord or brain in rat models of inflammation), and GW274150, a novel and highly selective inhibitor of the iNOS, shows analgesic effects in rat models of inflammatory and neuropathic pain [174]. Gap junctions are the site of exchange and communication between cells and are believed to be involved in peripheral sensitization. An event called "the augmented glial coupling" in dorsal root ganglion (DRG) following inflammation seems to contribute to a chronic pain. Intraperitoneal injection of a gap junction blocker "carbenoxolone" prevented the inflammation-induced decrease in pain threshold [232]. It seems that inflammation increases the communication and the cross talk between the glial and neuronal cells. Analysis of the DRG showed no coupling between neurons or between neurons and satellite glial cells (SGCs) in normal tissues, however, in a mouse model of inflammation using complete Freund's adjuvant (CFA) induced sciatic nerve neuritis, after CFA application the incidence of neuron-neuron and neuron-SGC coupling was 8% (significantly increased). Electron microscopy showed formation of bridges between SGC sheaths surrounding different neurons, which were completely absent in controls and the mean number of gap junctions occupied by SGCs increased more than 3 times in the CFA-treated mice [233]. As mentioned earlier, tonabersat a gap junction/ CSD inhibitor drug in its phase II, showed a preventive effect on attacks of migraine aura but no efficacy on non-aura attacks [36].

Therefore, peripheral sensitization which involves several inflammatory mediators is an important phenomenon aggravating the pain of migraine and various anti-inflammatory drugs are effective treatment in general for pain and in particular for the peripheral sensitization. However, other medication could potentially be effective in decreasing the peripheral sensitization.

Central Sensitization

In addition to the peripheral sensitization, the central sensitizations can also lead to heightened state of pain and should be considered as an important factor when treating the headache.. Central sensitization involves an increase in the excitability of medullary dorsal horn (subnucleus caudalis) and spinal dorsal horn neurons due to several conditions including the neuronal depolarization, removal of the voltage-dependent magnesium block of the N-methyl-D-aspartate (NMDA) receptor, release of calcium from intracellular stores, phosphorylation of the NMDA, as well as the alpha amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA), and the NK-1 receptors via activation of protein kinases, as well as a change in the neuron's excitability and an increase in synaptic strength, where several neurotransmitters/ neuromodulators are implicated [127, 128, 234], although these occur predominantly with structural changes such as the neuropathic pain. Central sensitisation may cause a prolonged increase in the excitability of dorsal horn neurons and contribute to the generation of pain by previously non-painful stimuli (allodynia), to exacerbated pain responses to previously painful stimuli (hyperalgesia) and to spontaneous pain conditions [127].

The central axons of primary afferent C-fibers contain and release peptides including the CGRP and SP, as well as excitatory amino acid such as the glutamate that can activate the 2^{nd} order neurons. For glutamate, direct monosynaptic excitation is mediated by non-NMDA receptors i.e. acute primary afferent excitation of wide dynamic range (WDR) neurons is not mediated by the NMDA or tachykinin NK1 receptor [128]. The interneurons are also excited by primary afferents which induce excitation in second-order neurons, however, via an NMDA receptor, increasing the intracellular Ca^{+2}, which leads to the activation of phospholipase A2, NOS and phosphorylating enzymes. The COX products, PGs and NO are formed in the dorsal horn 2^{nd} order neurons and diffuse locally into the extracellular space and facilitate transmitter release (retrograde transmission) from primary and non-primary afferent terminals either by a direct cellular action (e.g. NO) or by an interaction with the "EP" prostanoid receptors, which leads to additional enhanced sensitivity in the dorsal horn [128].

Cutaneous allodynia seen in some migraine patients is a manifestation of sensitization of central trigeminovascular neurons. Single-unit recordings from spinal trigeminal neurons that proved to receive convergent inputs from the dura and facial skin revealed that early treatment with triptan prevents the initiation of central sensitization triggered by chemical stimulation of meningeal nociceptors. However, in the late treatment, triptan action was insufficient to counteract an already established central sensitization [226].

For many migraine patients, triptan therapy provides complete pain relief in some attacks but not in others. A clinical study testing the ability of triptan therapy to treat migraine pain in the presence of cutaneous allodynia (pain resulting from a nonnoxious stimulus to normal skin), a phenomenon which develops gradually during the course of the migraine attack in more than 70% of patients, revealed that although the early treatment with triptan prevents the initiation of central sensitization triggered by chemical stimulation of meningeal nociceptors, the late treatment is insufficient to counteract an already established central sensitization. For patients susceptible to allodynia during the attack, triptan therapy was by far more likely to provide complete pain relief if administered before rather than after the establishment of cutaneous allodynia [235].

However, migraine attacks associated with periorbital allodynia (a symptom of central sensitization) unaffected to triptan therapy were readily terminated by subsequent i.v. administration of the NSAID. Infusion of COX-1/COX-2 inhibitors (ketorolac, indomethacin) stops migraine in allodynic patients, and also suppresses the ongoing sensitization in central trigeminovascular neurons in the rat. Therefore, migraine with ongoing allodynia can be terminated with NSAIDs using COX-1/COX-2 inhibitors by suppression of the central sensitization [236]. Parenteral administration of naproxen, unlike triptan therapy, can exert direct inhibition over central trigeminovascular neurons in the dorsal horn [237].

Indeed in one of our studies, electrical stimulation of trigeminal ganglion in the rat increased c-fos expression in the CTN, however, intravenous administration of sumatriptan 30 minutes prior to the attack failed to decrease c-fos activity in the CTN [111], but seemed to block the CGRP release from peripheral axons in the rat dura mater. There are reports however, indicating a poor penetration of sumatriptan through the blood brain barrier [238-240], since other triptans as well as dihydroergotamine are able to inhibit the activation of CTN in animals undergoing superior sagittal or dural stimulation [241-243]. This was consistent with the persistent activation of the brainstem after migraine attack [40] even after sumatriptan relieved the headache. Indeed such activation of brainstem is behind the belief that migraine might be a brain disorder and a failure of proper sensory transmission.

Central sensitization is an important phenomenon which can aggravate the headache symptoms, and NSAIDs are able to relief headache symptoms.

Glutamate receptors might represent a promising target for a valuable, non-vasoconstrictor, and perhaps more importantly neuronal-specific therapeutic approach to the treatment of migraine [244], but side effects of some receptors should also be considered [127].

What are the Current Recommendations for Treatment of Primary Headache?

The focus of this review was more on the NSAIDs, otherwise, various other treatment options for migraine include triptans, ergot alkaloids, antidepressants, anti-epileptic drugs, antihypertensive medication and natural supplements, see the following for review [11, 13, 87, 96-98, 102, 245]. A very useful short review of the new drugs under clinical trials for the prevention and treatment of migraine is available [175]. Various drugs for the treatment of acute attack including the CGRP receptor antagonists, telcagepant and Bl 44370, the 5-HT_{1F} receptor agonist (COL-144), the transient receptor potential vanilloid type 1 (TRPV1) receptor antagonists including SB-705498, AMPA and kainite receptor (including the GLUK5) antagonists, the prostanoid EP_4 receptor antagonist BGC20-1531, and nNOS inhibition and 5-$HT_{1B/D}$ agonist

(NXN-188) [175]. These are partially in consistent with the idea that the immediate future preventive treatment for migraine headaches may include the botulinum toxin type-A, glutamate NMDA receptor antagonists, gap-junction blocker tonabersat and an angiotensin type 1 blocker candesartan, while the future compounds for the treatment of acute migraine headaches include TPRV1 antagonists, PGE receptor 4 (EP_4 receptor) antagonists, serotonin $5HT_{1F}$ receptor agonists and NOS inhibitors [246]. Nevertheless, early treatment of primary headache disorders is important in order to prevent structural changes in the brain and to minimize dysfunction in the descending modulation of pain control [192, 247].

The European Federation of Neurological Societies (EFNS) guidelines by the members of the task force resulted in level A, B, or C recommendations and good practice points, the following treatment strategies are the widely accepted approaches: For the acute treatment of migraine attacks, oral NSAIDs and triptans are recommended. The administration should follow the concept of stratified treatment. Before intake of NSAIDs and triptans, oral metoclopramide or domperidon (anti-emetic drugs) is recommended. In very severe attacks, intravenous acetylsalicylic acid or subcutaneous sumatriptan are drugs of first choice. A status migrainosus can probably be treated by steroids. For the prophylaxis of migraine, β-blockers (propranolol and metoprolol), flunarizine, valproic acid, and topiramate are drugs of first choice. Drugs of second choice for migraine prophylaxis are amitriptyline, naproxen, petasites, and bisoprolol [14].

Therefore, during the headache phase (which might be accompanied by nausea and vomiting) and is believed to be associated with cerebral vasodilation and possibly neurogenic inflammation mediated by release of neuropeptides, various routs of administration of analgesics such as NSAIDs as well as the triptans is recommended.

The cortical spreading depression (CSD) provides a common therapeutic target for widely prescribed migraine prophylactic drugs including the anti-epileptic and antihypertensive drugs, and antidepressants. Chronic daily administration of these migraine prophylactic drugs in rats dose-dependently suppressed CSD frequency by 40 to 80% [248], and tonabersat (a gap junction/ CSD inhibitor) showed a preventive effect on attacks of migraine aura but no efficacy on non-aura attacks [36]. Oral triptans outperform oral ergotamine most because of the extremely low (< 1%) oral bioavailability of ergotamine. Comparing the triptans with the NSAIDs, they are not, in most cases, superior to aspirin, while additional advantage of aspirin is that it is also cheaper than triptans. Aspirin is being suggested as the first-choice drug in migraine treatment [102]. A comparison between various recommended drugs for the treatment of migraine and the influence of excessive acute medication use on the development of chronic migraine indicates that the progression of migraine to chronic state depends upon within-person characteristics (eg, headache frequency), class of drug, and frequency of medication use [249]. The use of opioids and barbiturates in treatment of migraine lead to chronification (progression) of migraine, and the effect is dose dependent. Triptans induce migraine progression only in those with high migraine frequency at baseline (10-14 days per month), but not overall. The NSAIDs, however, protect against migraine progression unless individuals have 10 or more headache days per month (when they become inducers of pain, rather than protective) [221, 249]. There are several non-pharmacological and nutritional supplement therapies for the treatment of migraine, see Linde 2006 [11] and [250] for review please.

Analyzing data from several clinical studies shows that Ibuprofen 200 and 400 mg are effective in reducing headache intensity and rendering patients pain-free at 2 hours. Photophobia and phonophobia improved with 400 mg dosing, although data and evidence were limited [251].

A recent study analyzed the frequencies of all and GI adverse events (AEs) and adverse drug reactions (ADRs) from nine clinical trials of single-doses of aspirin (1000 mg) in the treatment of acute migraine attacks, episodic tension-type headache and dental pain. Their results indicates that AE rates were 14.9% and 11.1% amongst patients allocated to aspirin and placebo respectively (numbers-needed-to-harm "NNH": 26), with the GI system most frequently affected (aspirin: 5.9%; placebo: 3.5%; NNH: 42). The study also finds that the reported ADR rates were much lower (aspirin: 6.3%; placebo: 3.9%; NNH: 42), especially for the GI system (aspirin: 3.1%; placebo: 2.0%; NNH: 91) and most of the AEs and ADRs were mild or moderate, and none was serious. They conclude that the GI ADR differences between aspirin and placebo are not great enough to support decision choices for short-lasting acute pain based on tolerability: these are better based on efficacy [252].

A recent study analyzing the adverse effect of NSAIDs used for common cold within the last decades found no evidence of increased frequency of adverse effects in the NSAID treatment groups [253].

Nevertheless, a high frequency of adverse events is also reported in patients who receive the placebo compared to the painkiller under evaluation in analgesic clinical trials. A recent systematic review study analyzing this issue found that the rate of adverse events in the placebo arms of trials with anti-migraine drugs was high, and suggests that the adverse events in placebo arms of clinical trials of anti-migraine medications depend on the adverse events of the active medication against which the placebo is compared [254].

Treatment of tension type headache (TTH) includes the reassurance and attempts to reduce stress and analgesic over-use. Although CGRP receptor antagonists may be helpful in treatment of a subpopulation of the TTH patients, the tricyclic antidepressant drugs have been used traditionally. For acute treatment, simple analgesics and NSAIDs are the most commonly used drugs that are often taken by the patient without a prescription. For preventive treatment, amitriptyline is the best-studied drug, but nortriptyline, mirtazapine, tizanidine, the selective serotonin reuptake inhibitors, and other medications are also suggested [255]. Nevertheless, non-pharmacologic, complementary and alternative approaches to TTH treatment including psychological therapies, acupuncture, and physical treatments are also available [256].

Table 1. Selected Chemical/Inflammatory Mediators Involved in the Pathogenesis of Headache, and Selected Drugs Regulating their Function, and the Mechanism of Action of the Drug and Some Importance Side Effects

Chemical Mediator Involved in Headache	Drug	Mechanism of Drug Action and Side Effects
Serotonin	Triptans	5-$HT_{1B/D}$ agonists, very effective anti migraine drugs, constrict blood vessels including the coronary arteries [a].
Serotonin	Ergot alkaloids	Affinity for 5-$HT_{1B/D}$ receptors, but also other serotonin receptors, as well as adrenergic and dopaminergic receptors. Cause vascular effects, nausea, vomiting, muscle cramps, chest discomfort and others [b].
Serotonin	Pizotifen and others	Blocks 5-HT_2, 5-HT_{1C}, H_1, and muscarinic receptors. Have been used in the past, but limited use now due to adverse effects [c].
CGRP	Telcagepant and olcegepant	CGRP-receptor antagonists, possibly in the central nervous system rather than in the periphery or the trigeminal ganglion [d].
iNOS	GW274150	A novel highly selective inhibitor of iNOS in the peripheral tissues. It has analgesic effects in rat models of inflammatory and neuropathic pain. But it is not clear if it can prevent migraine in clinical trials [e].
Substance P	RPR100893	Neurokinin-1 receptor antagonist. Failed to alleviate the pain of migraine patients [f].
Somatostatin (SST)	Octreotide/SMS201-995 and long-acting somatostatin/ sustained-release-SST (sandostatin LAR)	Octreotide is a synthetic octapeptide analogue of somatostatin, blocked plasma protein extravasation within rat and/or guinea pig dura mater; a single dose of 100 micrograms given subcutaneously is an effective and well-tolerated agent for the treatment of migraine attacks [g]. Somatostatin analogues may be highly effective in aborting headache associated with functionally active pituitary lesions by inhibiting nociceptive peptides, and treating meningiomas by sandostatin LAR [h].
Somatostatin	Cyclo-somatostatin	This SST-antagonist injection into the posterior hypothalamus of the rat decreased the A- and C-fiber responses to dural stimulation, leading to decreased spontaneous activity probably mediated via GABAergic mechanisms [i].
Presynaptic Ca^{++} influx and postsynaptic K^+ efflux	Opiates	Activation of opioid receptors decreases Ca^{++} influx into the neuron, which decreases excitatory neurotransmitter release from primary afferents. Opiates can also hyperpolarize the postsynaptic neurons in the medullary dorsal horn by activating the K^+ conductance outward (efflux), decreasing the intracellular positive charges [j], thus decreasing the response of the postsynaptic neurons to excitatory stimuli. Side effects include increased risk of transformed migraine and other side effects [k].
Prostaglandins and other inflammatory mediators	NSAIDs	Blocking the cyclooxygenase and other pathways [l]. Several side effects including gastrointestinal disturbances.

Table 1 is the summary of most of the chemical/ inflammatory mediators and neuropeptides involved in the pathogenesis of headache discussed in this review. Only selected substances with a link to inflammation which favors the aim of this review were mentioned.

[a b c] serotonin receptor agonists are widely used in the treatment of migraine, but serotonin receptor antagonists were also used [83, 86, 87, 94, 96, 99, 250];

[d] the CGRP receptor antagonists are novel promising anti-migraine drugs in phase II and III clinical trials [154- 158];

[e] the iNOS inhibitor might be helpful for the treatment of migraine but clinical trials should prove this [174] and [http://clinicaltrials.gov/ct2/show/NCT00319137];

[f] the SP-antagonist were not effective anti-migraine drugs [180- 182];

[g, h] somatostatin [189, 190, 197,198] and for cyclo-somatostatin [i] [196];

[j] activating the opioid receptors can inhibit the presynaptic Ca^{++} influx and postsynaptic K^+ efflux [200, 220], [k] see [221] for opiates side effects in headache;

[l] the NSAIDs act by inhibiting the synthesis of prostaglandins [220] and are effective first choice drugs in the treatment of migraine headaches [14].

Treatment of cluster headache (CH) includes the ergotamine and sumatriptan, oxygen inhalation, locally applied anesthetic agents, and prednisolone. For prevention and prophylactic treatment, the methysergide, calcium channel blockers, or lithium bicarbonate are being used [54]. As mentioned before, blood VIP levels increase during chronic paroxysmal hemicrania (CPH) attacks, and can be normalized by indomethacin treatment [257].

The VIP seems to mediate the facial symptoms such as nasal congestion and rhinorrhea [73], and influences the cerebral arteries and brain haemodynamics in cluster headache and in chronic paroxysmal headache. Molecular cloning of pituitary adenylate cyclase-activating polypeptide (PACAP) receptors has shown the existence of three distinct receptor subtypes: the PACAP-specific PAC1-R, which is coupled to several transduction systems, and the PACAP/VIP-indifferent VPAC1-R and VPAC2-R, which are primarily coupled to adenylyl cyclase [258]. Infusion of VIP in migraine patients mediates a marked dilation of cranial arteries, but does not trigger migraine attacks [259] or causes a very mild headache [260]. Parasympathetic activation releases a mixture of signaling molecules including

vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP), which subsequently stimulate VPAC(1), VPAC(2) and PAC(1) receptors; a recent experiment measuring rat middle meningeal artery (MMA) diameter using the closed cranial window model shows that the VPAC(1) receptor seems to be predominant in mediating MMA dilation [261] suggesting a selective VPAC(1) antagonist may help against vasodilation in headaches. Nevertheless, the role of VIP or PACAP, as well as the dilation of the MMA as triggers for migraine are not clear [3].

Table **1**, is a summary of most important chemical and inflammatory mediators involved in headache and drugs regulating their function and their mechanism of action.

CONCLUSION

Apart from many proposed pathogenesis of primary headaches including the migraine, peripheral and central sensitization are complications of the pain processing network that may aggravate the headache and involve other molecules including the inflammatory mediators. Anti-inflammatory drugs play a significant role in the treatment of headache. The recommended first choice drugs for the treatment of acute migraine are the NSAIDs and triptans (5-$HT_{1B/D}$ receptor agonists). Even for very severe attacks, intravenous acetylsalicylic acid or subcutaneous sumatriptan are drugs of first choice, and steroids can probably treat a status migrainosus. Still aspirin is considered to be the first-choice drug in migraine treatment [102]. Opioids and dihydroergotamine (a vasoconstrictor, acting on 5-$HT_{1B/D}$ receptors) are being used to treat headaches, have been discussed in this article. Opioids and barbiturate lead to chronification (progression) of migraine [249]. Several preventive medications including the beta-blockers and anti-epileptic drugs, antidepressants, and calcium channel blockers are among the recommended drugs for the prophylaxis of migraine [14, 250]. Serotonin receptor antagonists, angiotensin converting enzyme inhibitors, atypical antipsychotic drugs, antileukotriene drugs, and melatonin have also been implicated in the prevention of migraine [250], although their role may need more investigation [82]. Among various neuropeptides implicated in the pathogenesis of migraine, increase CGRP level has been detected in the serum of migraine patients. Newly discovered CGRP receptor antagonists, the olcegepant and telcagepant seem to be very promising drugs in treating acute migraine [154-158]. Various future drugs for the treatment of acute attack may include the 5-HT_{1F} receptor agonist, the transient receptor potential vanilloid type 1 (TRPV1) receptor antagonists, AMPA and kainite receptor antagonists, the prostanoid EP4 receptor antagonist, and nNOS inhibition are under investigation[175], while future preventative treatment for migraine headaches may include the botulinum toxin type-A, glutamate NMDA receptor antagonists, gap-junction blocker tonabersat and an angiotensin type 1 blocker candesartan [246, 250]. Nevertheless, anti-inflammatory drugs continue to remain the first choice strong and cost effective drug in treatment of migraine. Drugs used for cluster and tension type headaches have been discussed. Yet, there are several non-pharmacological therapies for headache [11, 250, 256].

ABBREVIATIONS

ASICs	=	Acid-sensing ion channels
ATP	=	Adenosine triphosphate
ADRs	=	Adverse drug reactions
AEs	=	Adverse events
AMPA	=	Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
CGRP	=	Calcitonin gene-related peptides
CRL	=	Calcitonin receptor-like receptor
CTN	=	Caudal trigeminal nucleus
CCK	=	Cholecystokinin
CPH	=	Chronic paroxysmal hemicrania
CH	=	Cluster headache
CNS	=	Central nervous system
CSD	=	Cortical spreading depression
CSF	=	Cerebrospinal fluid
cAMP	=	Cyclic adenosine monophosphate
cGMP	=	Cyclic guanosine monophosphate
COX	=	Cyclooxygenase
DHE	=	Dihydroergotamine
DRG	=	Dorsal root ganglion
EP_4	=	E prostanoid 4
CFA	=	Freund's adjuvant
GABA	=	Gamma aminobutyric acid
GTN	=	Glyceryl trinitrate
TRPV1	=	Transient receptor potential vanilloid type 1
IL-1	=	Interleukin-1
MMA	=	Methionine- enkephalin (Met-Enk) middle meningeal artery
MAPK	=	Mitogen-activated protein kinase
NMDA	=	N-methyl-D-aspartate
NKA	=	Neurokinin A
NPY	=	Nuropeptide Y
NO	=	Nitric oxide
NOS	=	Nitric oxide synthase
NSAIDs	=	Inducible NOS (iNOS) non-steroid anti-inflammatory drugs
NNH	=	Numbers-needed-to-harm
PH	=	Paroxysmal hemicrania
PET	=	Positron emission tomography
PACAP	=	Pituitary adenylate cyclase-activating polypeptide
PG	=	Prostaglandin

(PKC)/(PKA)	=	Protein kinase –C/ -A
TTH	=	Tension type headache
PAG	=	Periaqueductal gray
RAMP1	=	Receptor activity-modifying protein 1
rCBF	=	Regional cerebral blood flow
SGCs	=	Satellite glial cells
5-HT	=	Serotonin
SUNCT	=	Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing
SST	=	Somatostatin
SP	=	Substance p
TAC	=	Trigeminal autonomic cephalalgia
TG	=	Trigeminal ganglion
TNFα	=	Tumor necrosis factor-alpha
VR1	=	Vanilloid receptor
VIP	=	Vasoactive intestinal peptide

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