Migraine: Current concepts and emerging therapies

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Abstract

Migraine is a recurrent incapacitating neurovascular disorder characterized by attacks of debilitating pain associated with photophobia, phonophobia, nausea and vomiting. Migraine affects a substantial fraction of world population and is a major cause of disability in the work place. Though the pathophysiology of migraine is still unclear three major theories proposed with regard to the mechanisms of migraine are vascular (due to cerebral vasodilatation), neurological (abnormal neurological firing which causes the spreading depression and migraine) and neurogenic dural inflammation (release of inflammatory neuropeptides). The modern understanding of the pathogenesis of migraine is based on the concept that it is a neurovascular disorder. The drugs used in the treatment of migraine either abolish the acute migraine headache or aim its prevention. The last decade has witnessed the advent of Sumatriptan and the Triptan class of 5-HT1B/1D receptor agonists which have well established efficacy in treating migraine. Currently prophylactic treatments for migraine include calcium channel blockers, 5-HT2 receptor antagonists, beta adrenoceptor blockers and GABA agonists. Unfortunately, many of these treatments are non specific and not always effective. Despite such progress, in view of the complexity of the etiology of migraine, it still remains undiagnosed and available therapies are underused. In this article, the diverse pieces of evidence that have linked the different theories of migraine with its pathophysiology are reviewed. Furthermore, the present therapeutic targets and futuristic approaches for the acute and prophylactic treatment of migraine, with a special emphasis to calcitonin gene-related peptide, are critically evaluated.

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Keywords: Migraine; CGRP; Serotonin; Triptan

1. Introduction

Migraine is a chronic, often debilitating disease that affects 12% of the general population. This episodic brain disorder is characterized by unilateral throbbing headache lasting from 4 h to 3 days. Associated symptoms include nausea vomiting and sensitivity to light, sound and head movements (Silberstein, 2004). A working definition of migraine is benign recurring headache and/or neurological dysfunction usually attended by pain-free interludes and often provoked by stereotyped stimuli. Migraine is more common in females, with a hereditary predisposition towards attacks and the cranial circulatory phenomenon appears to be secondary to a primary central nervous system disorder.

The Headache Classification Committee of the International Headache Society (IHS) published the classification and diagnostic criteria for headache disorders (International Headache Society, 2004). The terms ‘common migraine’ and ‘classical migraine’ have been replaced by ‘migraine without aura’ and ‘migraine with aura’ respectively. These operational criteria have been validated by different approaches and have enabled to distinguish different headache entities in a reliable manner.

Migraine apparently a global disorder, occurring in all races, cultures and geographical locations. Current figures suggest that 18% of women and six percent of men suffer from migraine and those numbers are increasing. The Center for Disease Control reported a 60% increase in the disease
from 1980 to 1989. The highest incidence of migraine occurs between the ages of 20 and 35 and often associated with a positive family history of the disease (Lipton and Bigal, 2005).

Migraine has an enormous impact on society. Recent studies have evaluated the indirect and direct costs of migraine. Indirect costs include the aggregate effects of migraine on productivity at work (paid employment), in performance of household work and in other roles. It was estimated that productivity losses due to migraine cost American employers $13 billion per year (Lipton et al., 2003).

In the present review, the modern theories of migraine with respect to its diverse etiology as well the present therapeutic targets and futuristic approaches for the acute and prophylactic treatment of migraine are critically evaluated.

2. Pathophysiology of migraine

2.1. Clinical manifestations

Migraine is characterized by episodes of head pain that is often throbbing and frequently unilateral and may be severe. In migraine without aura (previously known as common migraine) attacks are usually associated with nausea, vomiting, or sensitivity to light, sound, or movement and when treated, the attacks typically last 4 to 72 h (Olesen and Lipton, 1994; Michel et al., 1993). A combination of features is required for the diagnosis, but not all features are present in every attack or in every patient (Tables 1 and 2). These symptoms do distinguish migraine from tension type headache, the most common form of primary headache, which is characterized by the lack of associated features (Silberstein, 2004). Any severe and recurrent headache is most likely a form of migraine and should be responsive to antimigraine therapy (Lance, 2000). In 15% of patients migraine attacks are usually preceded or accompanied by transient focal neurotic symptoms, which are usually visual; such patients have migraine with aura (previously known as classic migraine) (Rasmussen et al., 1992; Rasmussen and Olesen, 1992). In a recent, large population-based study, 64% of patients with migraine had only migraine without aura, 18% had only migraine with aura and 13% had both types of migraine (the remaining 5% had aura without headache). Thus, up to 31% of patients with migraine have aura on some occasions (Launer et al., 1999), but clinicians who rely on the presence of aura for the diagnosis of migraine will miss many cases.

A recent survey by the World Health Organization (WHO), rates severe migraine, along with quadriplegia, psychosis, and dementia, as one of the most disabling chronic disorders (Menken et al., 2000). This ranking suggests that in the judgment of WHO, a day with severe migraine is a disabling as a day with quadriplegia.

Table 1
Diagnostic criteria of migraine

Migraine without aura
A. At least 5 attacks fulfilling B–D
B. Headache attacks, lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics
1. Unilateral localization
2. Pulsating quality
3. Moderate to severe intensity
4. Aggravation by walking stairs or similar routine physical activity
D. During headache at least one of the following
1. Nausea and/or vomiting
2. Photophobia and phonophobia
E. At least one of the following
1. History, physical- and neurological examinations do not suggest association with head trauma, vascular or non-vascular disorders, use of or withdrawal from noxious substances, non-cephalic infections, metabolic disorders or disorder or cranial or facial structures
2. History and/or physical- and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations
3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation with the disorder

Migraine with aura
A. At least 2 attacks fulfilling B
B. Migraine aura fulfills criteria for typical aura, hemiplegic aura, or basilar-type aura
C. Not attributed to another disorder

Typical aura
1. Fully reversible visual, sensory, or speech symptoms (or any combination) but no motor weakness
2. Homonymous or bilateral visual symptoms including positive features (eg. Flicking of lights, spots, lines) or negative features (e.g. Loss of vision), or unilateral sensory symptoms including positive features (e.g. Visual loss, pins and needles) or negative features (e.g. Numbness), or any combination
3. At least one of
   a. At least one symptom develops gradually over a minimum of 5 min or different symptoms occur in succession or both
   b. Each symptom lasts for at least 5 min and for no longer than 60 min
4. Headache that meets criteria for migraine without aura begins during the aura or follows aura within 60 min

2.2. Genetics of migraine

Migraine is best understood as primary disorder of pain (Silberstein, 2004). It is a form of neurovascular headache: a disorder in which neural events result in the dilation of blood vessels, which in turn, results in pain and further nerve activation (Goadsby, 2001). Migraine is not caused by primary vascular event. Migraine attacks are episodic and vary within and among the individuals. The variability is best explained by considering the biologic problem in migraine to be the dysfunction of an ion channel in the aminergic brain stem nuclei that normally modulates sensory input and exerts neural influences on cranial vessels (Silberstein, 2004). There is thus ample evidence for genetic liability of migraine. Missense mutations in CACNA1A gene, coding for the alpha subunit of a neuronal P/Q type Ca$^{2+}$ channel were discovered in patients
with familial hemiplegic migraine (Montagna, 2004; Oph-off et al., 1996). It is possible that other ion-channel mutations contribute to migraine without aura, since it is primarily consist of patients of migraine with aura who have been linked to the familial hemiplegic migraine locus (Terwindt et al., 2001).

The second gene responsible for familial hemiplegic migraine was discovered to consist of the alpha 2 subunit of the Na/K pump gene linked to chromosome 1q23. The sodium-potassium pump catalyses the energy dependent transport of Na$^+$ and K$^+$ across the cell membrane and is a heterodimer, composed of a catalytic and a glycoprotein subunit. Two mechanisms were hypothesized to account for an altered excitability of the membrane in mutated cells; an increase in extra cellular K$^+$ because of impaired clearance of K$^+$ might induce cortical depolarization and facilitate a spreading depression (Montagna, 2004).

3. Theories of migraine

3.1. Vascular theory

In the late 1930’s, Harold Wolff became the first researcher to place migraine on a scientific basis, Wolf measured the diameter of the extracranial (temporal) arteries in patients suffering migraine attacks and found them to be dilated. These patients were treated with vasoconstrictors (ergotamine) which relieved the pain (Tables 2 and 3) and decreased the arterial dilation (Graham and Wolf, 1938).

Although subsequent events leading to headache (and associated symptoms) are not completely understood, the increased vascular pulsation may activate stretch receptors. This would, in turn increase the activity of neuropeptide containing (mainly calcitonin gene-related peptide (CGRP) perivascular nerves which may ultimately cause pain and other associated symptoms (De Vries et al., 1999; Willems et al., 2003).

In line with the finding that carotid arteriovenous anastomoses dilatation play a role in the pathogenesis of migraine, it is reasonable to believe that compounds which produce a cranioselective vasoconstriction may have a potential therapeutic use in the treatment of migraine. In anaesthetized dogs and pigs acutely acting antimigraine drugs, ergot alkaloids and dihydroergotamine (sumatriptan and second generation triptans) produced potent vasoconstriction in the canine and porcine carotid vasculature (De Vries et al., 1996). Further studies demonstrated that mainly 5-HT_{1B} receptors mediate sumatriptan-induced cranial vasoconstriction, involving carotid arteriovenous anastomoses and temporal and middle meningeal arteries (De Vries et al., 1998).

3.2. Neurological theory

A second theory of migraine is the neurological theory of migraine. This theory suggests that migraine arises as a result of abnormal neuronal firing and neurotransmitter release in brain neurons. This theory focuses on an explanation for certain symptoms, such as premonitory symptoms occurring prior to an attack (prodrome), which are difficult to explain based on the vascular hypothesis. The fact that migraine headaches begin and develop slowly coupled to the fact that external factors, such as stress, and hunger can precipitate migraine attacks to pathologies arising in the neuronal system, thus supporting a neurological basis of migraine (Pearce, 1984). Cortical spreading depression, an expanding depolarization of cortical neurons which is well characterized in many species but not in man is often suggested to underlie the aura or prodrome associated with initiation of migraine attack. During spreading depression, cortical function is disrupted subsequent to neuronal depolarization and increased extracellular potassium. These cortical changes are thought to be the cause of the transient sensory or motor impairments that frequently precede the painful period of a migraine attack.

Many investigators hypothesize that neuronal activation in migraine may be mediated by cortical spreading depression (CSD). In brief, CSD is a phenomenon of neuronal activation

### Table 2

<table>
<thead>
<tr>
<th>Migraine treatment strategies</th>
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<tbody>
<tr>
<td>Suppressing initiation and perpetuation of cortical spreading depression</td>
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<tr>
<td>Inhibiting mechanism of neurovascular coupling neurogenic inflammation</td>
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<tr>
<td>Inhibiting nociceptor activation</td>
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<td>Enhancing descending modulation</td>
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<td>Blocking peripheral and central sensitization</td>
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### Table 3

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<tr>
<th>Acute antimigraine agents</th>
<th>Contraindications</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Acetylaminoephene</td>
<td>Liver disease</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Kidney disease, ulcer disease, peptic ulcer disease, coronary artery disease, peripheral vascular disease, arthritis</td>
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<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Kidney disease, peptic ulcer disease, confirmed gastritis</td>
<td></td>
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<tr>
<td>Butalbital, Caffeine, and analgesics</td>
<td>Use of other sedative, history of medication overuse</td>
<td></td>
</tr>
<tr>
<td>Caffeine</td>
<td>Sensitivity to caffeine</td>
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</tr>
<tr>
<td>Ergotamine</td>
<td>Sensitivity to caffeine</td>
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<tr>
<td>Opioids</td>
<td>Drug or substance misuse</td>
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<tr>
<td>Neuroleptics</td>
<td>Parkinsons disease, uncontrolled hypertension</td>
<td></td>
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<tr>
<td>Dihydroergotamine inj and intranasal</td>
<td>Coronary artery disease, peripheral vascular disease, uncontrolled hypertension</td>
<td></td>
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<tr>
<td>Ergotamine Triptans</td>
<td>Coronary artery disease, prolonged Qtc</td>
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### Table 1

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<th>Drugs for acute migraine attacks</th>
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<tr>
<td>Acetaminophen</td>
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<tr>
<td>Aspirin</td>
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<td>Nonsteroidal anti-inflammatory drugs</td>
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<td>Neuroleptics</td>
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<td>Dihydroergotamine inj and intranasal</td>
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<td>Ergotamine Triptans</td>
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followed by suppression, which progresses over the cortical surface and spreads down into the depth of the sulci at a rate of 2–8 mm/min. Coupled with this electrical phenomenon are cerebral blood flow changes that manifest as initial hyperemia followed by spreading oligemia. Experimentally, CSD can be triggered by trauma and by chemicals such as hydrogen ions, potassium, and glutamate. The coupling between CSD and activation of the vascular nociceptives is not fully elucidated. Potential culprits include release of nitric oxide (NO) and atrionatriuretic factor (ANP), spread of astrocytic calcium waves to pial arachnoid cells with subsequent activation of intradural nociceptives, descending activation of noradrenergic pathways, changes in blood flow, and vascular dilatation with nociceptive sensitization (Lashley, 1941; Lashley et al., 1981; Olesen et al., 1981).

Several inconsistencies exist with the neurological theory of migraine. In part, these are related to the fact that the brain itself does not contain pain sensory fibers although pain fibers are located in the meninges. Furthermore, although stress may precipitate migraine, the actual occurrence of the headache pain generally prevails after, rather than during the stressful circumstance.

3.3. Neurogenic theory

Lance et al. (1983) demonstrated that blood flow changes similar to those known to occur in migraine could be produced by electrically stimulating brain stem structures. This finding led to the neurogenic theory. Stimulation studies investigated the relationship between the trigeminal nerve and the cranial vasculature. Moskowitz (1992) showed that trigeminovascular axons from blood vessels of the pia mater and dura mater release vasoactive peptides producing a sterile inflammatory reaction with pain. During this neurogenic inflammation, the trigeminal ganglion is stimulated and this induces neurogenic protein extravasation. Vasodilatory peptides then released, including calcitonin gene related peptide (CGRP), substance P (SP) and neurokinin A.

Neurogenic theory is an attempt to reconcile the vascular changes in the neuronal dysfunction that may occur in migraine headache and proposes that migraine pain is associated with inflammation and dilation of the meninges, particularly the dura, a membrane surrounding the brain. Neurogenic dural inflammation is thought to result from the actions of inflammatory neuropeptides released from the primary sensory nerve terminals innervating the dural blood vessels. In fact, the dural membrane surrounding the brain is the source for the majority of intracranial pain afferents and dural stimulation produces headache like pain in human (Moskowitz, 1992, 1993). Stimulation or inflammation of sensory fibers release the inflammatory neuropeptides, substance P and calcitonin gene-related peptide onto dural tissue, where these peptides produce a local response called neurogenic inflammation. Neurogenic inflammation may lower the nociceptive threshold required to stimulate meningeal sensory fibers (Moskowitz, 1990). According to neurogenic dural inflammation theory of migraine, release of these inflammatory neuropeptides in the dura mater during migraine can act on vascular tissues to cause vasodilatation, plasma protein extravasation in the surrounding area, endothelial changes, platelet aggregation and subsequent release of serotonin and other mediators, white cell adhesion and subsequent inflammation (Dimitriadou et al., 1991, 1992). CGRP plays a facilitatory role in this process (Brain and Williams, 1985). Whereas substance P induces extravasation via activation of NK1 receptors, release of CGRP enhances the effects of substance P by increasing dural blood flow and by inhibiting an extracellular enzyme that normally can metabolize substance P. Therefore, these two sensory neuropeptides act in concert to produce painful dural inflammation. Although not reliably demonstrated, increased cranial venous concentration of CGRP have been observed during a migraine attack and the elevated concentrations of CGRP have returned to normal following treatment of the migraine in the serotonergic agonists (Arulmani et al., 2004).

This theory is in consistent with the proposal that serotonergic agonist alleviate the acute pain of migraine by inhibiting the release of substance P and CGRP from trigeminal sensory afferent neurons surrounding the meninges.

4. Pain mechanisms in migraine

The pathogenesis of pain in migraine is not completely understood so far, but three key factors merit considerations are: the cranial blood vessels, the trigeminal innervation of the vessels, and the reflex connection of the trigeminal system in the cranial parasympathetic outflow. The substance of the brain is largely insensate; pain can be generated by large cranial vessels, proximal intracranial vessels or by the dura mater (Martin et al., 1993; Feindel et al., 1960). These vessels are innervated by branches of the ophthalmic division of the trigeminal nerve, whereas the structures of the posterior fossa are innervated by branches of the C2 nerve roots. In non-human primates, stimulation of vascular afferents leads to the activation of neurons in the superficial layers of the trigeminal nucleus caudalis in the region of the craniomandibular dysfunction junction and the superficial layers of the dorsal horns C1 and C2 levels of the spinal cord trigemino-cervical complex (Hoskin et al., 1999; Goadsby and Hoskin, 1997). Similarly, stimulation of branches of C2 activates neurons in the same regions of the brain (Kerr, 1960). The involvement of ophthalmic division of the trigeminal nerve and the overlap with structures innervated by C2 explain the common distribution of migraine pain over the frontal and temporal regions, as well as involvement of parietal, occipital and high cervical regions by what is, in essence, referred pain.

Peripheral trigeminal activation in migraine is evidenced by release of CGRP, a vasodilator (Goadsby et al., 1990),
but the mechanism of generation of pain is not clear. Studies in animals suggest that the pain may be caused by a sterile neurogenic inflammatory process in the dura mater (Moskowitz and Cutrer, 1993), but this mechanism has not been clearly demonstrated to correlate in humans (May et al., 1998). The pain may be a combination of an altered perception — as a result of peripheral or central sterilization of craniovascular input that is not usually painful (Burstein et al., 2000) and the activation of feed-forward neurovascular dilator mechanism that is functionally specific for the first (ophthalmic) division of the trigeminal nerve (May et al., 2001).

5. Serotonergic receptors and other pharmacological targets for potential antimigraine agents

Since long, it was observed that administration of 5-HT could abort migraine attacks. Further evidence that 5-HT is involved in the pathophysiology of migraine was provided by the observation that 5-HT metabolism in migraine patients is disturbed, interictal systemic 5-HT levels are reduced and raised during migraine attacks, possibly a (failing) self-defense response (Ferrari et al., 1990). These observations prompted the development of sumatriptan; the first migraine drug for which a specific molecular basis of action is known (Humphrey et al., 1990). Sumatriptan was designed to act selectively as a vasoconstrictor at 5-HT receptors in cranial blood vessels, but the drug also acts on 5-HT receptors located in peripheral human blood vessels. The exact mode of action of sumatriptan is still under debate.

Three distinct modes of action have been suggested (Ophoff et al., 2001; Ahn and Basbaum, 2005) are 1. Vasoconstriction of meningeal, dural, cerebral or pial vessels, mediated via stimulation of vascular 5-HT receptors. 2. Inhibition of dural neurogenic inflammation, most probably mediated by presynaptic stimulation of 5-HT and/or 5-HT receptors. 3. Central inhibition of pain transmission: inhibition of trigeminal neurons in the brain stems and upper spinal cord, mediated by 5-HT, 5-HT or 5-HT receptors.

5.1. 5-HT receptors

The antimigraine gold standard sumatriptan was originally identified and developed based on the vasodilatory theory of migraine and the hypothesis that constriction of the cerebral vascular smooth muscle would minimize the pain associated with migraine headache. Since the discovery of sumatriptan, intensive research in this area has led to several second generation compounds (Tables 4 and 5). These second generation triptans, though not much different from sumatriptan in their pharmacodynamics, have improved pharmacokinetics, higher oral bioavailability and in some cases, longer plasma half-life (Slassi et al., 2001).

5.2. 5-HT receptors

Though the triptans partly exert their antimigraine efficacy at least partly through cerebral vasoconstrictor effects (5-HT receptor mediated effect), triptans also inhibit neurotransmitter release from trigeminal nociceptive neurons (Table 7). Several triptans have modest to significant agonist activity 5-HT receptors. The ability of serotonergic receptor agonists to inhibit plasma protein extravasation in guinea pigs is correlated with their affinity to 5-HT receptors. In laboratory studies and preliminary clinical studies the 5-HT receptor agonist LY334370 found to be efficacious in acute migraine without associated vasoconstrictor effects observed with triptans, however subsequently the development of LY334370 has been discontinued due to poor efficacy in large trials. Further studies are warranted in order to better understand the link between 5-HT receptor and migraine with respect to clinical response to potential antimigraine therapies (Ramadan et al., 2003; Johnson et al., 1998).

5.3. 5-HT receptors

Recent observations suggested that nitric oxide generation and subsequent release of inflammatory neuropeptides (CGRP and substance P) from the trigeminal sensory nerve

<table>
<thead>
<tr>
<th>Company</th>
<th>Code name</th>
<th>Generic name</th>
<th>Trade name</th>
<th>Formulation</th>
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</thead>
<tbody>
<tr>
<td>Novartis</td>
<td>–</td>
<td>Dihydroergotamine</td>
<td>Migranal®</td>
<td>Nasal spray</td>
</tr>
<tr>
<td>Glaxo Wellcome</td>
<td>GR-43175</td>
<td>Sumatriptan</td>
<td>Imigrain®/Imitrex®</td>
<td>Nasal spray suppository</td>
</tr>
<tr>
<td></td>
<td>GR-85548</td>
<td>Naratriptan</td>
<td>Naramil®/Amerge®</td>
<td>Oral</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>BW-3111C-90</td>
<td>Zolmitriptan</td>
<td>Zomig®</td>
<td>Oral</td>
</tr>
<tr>
<td>Merck</td>
<td>L705126/MK-462</td>
<td>Rizatriptan</td>
<td>Maxalt®</td>
<td>Oral</td>
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<td>Maxalt melt</td>
<td>Oral lyso philate</td>
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<td>Pfizer</td>
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<td>Eletriptan</td>
<td>–</td>
<td>Oral</td>
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<td>SB-209509</td>
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<tr>
<td>Vanguard</td>
<td>VML-251</td>
<td>Frovatriptan</td>
<td>–</td>
<td>Oral</td>
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<td>Pharmacia</td>
<td>LAS-31416</td>
<td>Almotriptan</td>
<td>–</td>
<td>Oral, sc</td>
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<tr>
<td>Janssen</td>
<td>R-91274</td>
<td>Alniditan</td>
<td>–</td>
<td>Sc</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>BMS-180048</td>
<td>Avitriptan</td>
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</table>

Table 4
5-HT receptor agonists as antimigraine agents
may be associated with the initiation of migraine (Johnson et al., 1998). Furthermore, the 5-HT2B receptors on vascular endothelial cell have been linked to NO release (Schmuck et al., 1996). These observations coupled to the marked correlation between pharmacologically active doses of anti-migraine drugs and their potency at the human 5-HT2B receptor (Kalkman, 1994; Fozard and Kalkman, 1994; Fozard, 1995). It has been reported that 5-HT2B receptors in certain vascular endothelial beds can enhance nitric oxide release, which may diffuse from the endothelial cell to induce vasodilation and neuropeptide release. Thus the selective antagonism of 5-HT2B receptors would be effective in migraine prophylaxis (Johnson et al., 1998).

### 5.4. 5-HT7 receptors

Increasing data supports the concept that 5-HT7 receptor activation is responsible for the initial dilation of cerebral vessels and the subsequent activation of sensory pathways, consequent to neurogenic inflammation around the meningeal vessels, neural sensitization and activation of pain. Potential implications of the 5-HT7 receptor in cerebrovascular dilation, hyperalgesia and neurogenic inflammation might pave the way for new research efforts towards the understanding of migraine pathophysiological mechanism and drug development. The putative involvement of this receptor in the vascular and neurogenic alteration of migraine is consistent in the concept that the condition may result from massive release of 5-HT after abnormal activation of brainstem that is secondary to the hypothalamic dysfunctions (Fozard and Kalkman, 1994; Fozard, 1995) and the disease arises primarily from the neurovascular interaction (May and Goadsby, 1999). Admitting, despite the fact that the correlation analysis suggest the 5-HT7 receptor be a target for migraine prophylactic compounds, interpretation of their antimigraine effect in terms of blockade at this site is at present speculative. Clinical trials with selective 5-HT7 receptor antagonists, will be awaited with interest so the potential involvement of the 5-HT7 receptor in migraine pathogenesis and preventive treatment is elucidated (Terron, 2002).

### 5.5. α-adrenoceptors

It is believed that α-adrenoceptors could be involved in the vascular tone of carotid circulation, which may provide a potential avenue for the development of new antimigraine agents. It has been well established that several acutely acting antimigraine agents, including the ergots (ergotamine and dihydroergotamine) produce potent vasoconstriction in the canine and porcine carotid vasculature (De Vries et al., 1999). The canine carotid vasoconstrictor responses of these ergot alkaloids are mediated by 5-HT1D and 5-HT1B receptors. In addition, it results in delayed reduction in tyrosine hydroxylase activity, the

### Table 5

Selected pharmacologic characteristic of oral triptans

<table>
<thead>
<tr>
<th>Agent</th>
<th>Tmax during migraine</th>
<th>Bioavailability(%)</th>
<th>Route of metabolism</th>
<th>Plasma half life (h)</th>
<th>Drug interactions/precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naratriptan</td>
<td>3–4</td>
<td>70</td>
<td>CYP450 isoenzymes</td>
<td>6</td>
<td>No change in efficacy or adverse events when used with beta-blockers; efficacy not affected when used with oral contraceptives (OCs); observe patients when given with SSRIs; not contraindicated with MAO inhibitors</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>1.0–1.5</td>
<td>45</td>
<td>MAO-A</td>
<td>2–3</td>
<td>Concomitant use with propranolol increases triptan plasma levels and requires dose adjustment; no change in efficacy or adverse events when used with metoprolol, nadolol or OCs; observe patients when given with SSRIs; contraindicated with MAO inhibitors</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>2.5</td>
<td>15</td>
<td>2.5</td>
<td></td>
<td>Efficacy not affected when used with beta-blockers; observe patient when given with SSRIs; contraindicated with selective MAO-A and nonselective MAO inhibitors; not contraindicated with selective MAO-B inhibitors</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>2.5</td>
<td>40</td>
<td>CYP1A2/MAO-A</td>
<td>3</td>
<td>Concomitant use with propranolol increases plasma levels; no change in efficacy or adverse events when used with propranolol; observe patient when given with SSRIs; contraindicated with selective MAO-A and nonselective MAO inhibitors; not contraindicated with selective MAO-B inhibitors</td>
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</table>
rate-limiting step in norepinephrine synthesis, in the superior cervical ganglia. In the rat brain stem, a delayed reduction of the locus ceruleus neuronal firing rate has been demonstrated after propranolol administration (Hieble, 2000). This could explain the delay in the prophylactic effects of the β-blocker.

The action of β-blockers is probably central and could be mediated by: (i) inhibiting central β receptors interfering with vigilance-enhancing adrenergic pathway, (ii) interaction with 5-HT receptors (but not all β-blockers bind to 5-HT receptors), and (iii) cross-modulation of serotonin system (Ablad and Dahlof, 1986; Koella, 1985).

5.7. Calcium channels

The complex nature of the genetics of the common types of migraine has, however hampered the identification of an underlying genetic factor. The migraine spectra comprises the common types of migraine (with and without aura) as well as rate autosomal dominant variants of migraine with aura, associated with a transient hemiparesis or hemiplegia (one sided weakness or paralysis of the body) in addition to other aura symptoms. In some families, symptoms of familial hemiplegic migraine are also associated with (progressive) permanent ataxia (disturbance of co-ordination of movements). The symptoms of headache and aura phase of familial hemiplegic migraine and normal migraine attacks are very similar and both types may alternate within individuals and co-occur within families. These observations suggest strongly that familial hemiplegic migraine is part of the migraine spectrum and that familial hemiplegic migraine can be used as a model to study the complex genetics of common types of migraine. Importantly, familial hemiplegic migraine exhibits a clear autosomal dominant inheritance pattern, allowing conventional parametric linkage analysis to identify the chromosomal localization of genes causal to the syndrome in the specific family (Montagna, 2004; Ophoff et al., 1994, 1996).

In 50% of the familial hemiplegic migraine families, the causative genes encode the brain specific voltage gated Ca\(^{2+}\) channels α\(_{1A}\) subunit (CANCNA1A) (Stilberstein and Stilberstein, 1990; Ophoff et al., 1994, 1996) located on the short arm of chromosome 19. A number of remaining families have a locus on chromosome 1q21–q23 (Ducros et al., 1997; Gardner et al., 1997), where as other familial hemiplegic migraine families are lined to either chromosome 19p or 1q (Ducros et al., 1997). These results clearly show a genetic heterogeneity for familial hemiplegic migraine with at least three different genes involved only one, which has been yet identified.

5.8. Platelet serotonin release

Platelets have become an important etiological consideration in migraine, as they contain over 90% of the serotonin in the blood. Once they aggregate, platelets release serotonin, and other vasoactive chemicals causing potent vasoconstrictive effect. Platelet aggregation has been shown to be altered in migraine patients and raises the possibility that platelet activating factor may be involved in the pathogenesis of migraine (Kovac et al., 1998). It is demonstrated that, platelets of migraine patients showed abnormal tendencies toward hyperaggrability and reduced monoamine oxidase activity. There was significant correlation in this study between MAO activity and sensitivity to prostaglandins (Kovac et al., 1998). Even during headache free periods, migraine patients were shown to exhibit greater degree of platelet sensitivity to serotonin and adenosine di phosphate when compared to healthy controls (Lechner et al., 1985). Urinary serotonin metabolites have been shown to increase during the acute phase of migraine attacks. Other vasoactive constituents that may play a role in migraine include tyramine, histamine, plasmakinin, epinephrine and norepinephrine. Many nutritional and botanical therapies aim to decrease platelet aggregation to inhibit the release of inflammatory neurotransmitters.

6. Emerging therapies

6.1. Calcitonin gene-related peptide (CGRP) antagonists

In the recent past, there has been an upsurge in CGRP research and its notable role in migraine pathophysiology. As discussed above, migraine headache is closely associated with the activation of trigeminovascular system. CGRP immunoreactive fibres originating in the trigeminal ganglion innervate cranial cerebral blood vessels (Uddman et al., 1985). In animals, stimulation of these sensory nerve fibers has been shown to cause antidromic release of CGRP and subsequent vasodilatation in the cerebral vasculature (Goadsby et al., 1988; Brain and Grat, 2004). Plasma concentrations of CGRP in the jugular venous blood, but not of other neuropeptides was elevated during the headache phase of migraine (Durham, 2004a). Furthermore, in migraine patients: (a) strong correlation was found between plasma CGRP concentrations and migraine headache (b) infusion of CGRP produced a migraine-like headache (c) baseline CGRP levels were considerably higher and (d) the changes in plasma CGRP levels during migraine attacks significantly correlated with the headache intensity (Peterson et al., 2005a; Iovino et al., 2004; Durham, 2004b).

Recently Peterson et al. (2005b) has demonstrated a concentration dependent relaxation in the middle cerebral artery when CGRP was applied abluminally, which suggest that CGRP mediated vasodilatation is not caused by interaction with luminally situated receptor but more likely by abluminal receptor on the smooth muscle cells (Fig. 1). Hence, inhibition of CGRP or antagonism of CGRP receptors could be a viable therapeutic target for the pharmacological treatment of migraine (Edvinsson, 2004).
In line with this concept, an important breakthrough in the field of CGRP is the development of potent CGRP receptor antagonist olcegepant (BIBN4096BS). In the in vivo animal models of migraine, olcegepant attenuated the vasodilation induced by trigeminal stimulation and capsaicin-induced anastomotic dilatation (Peterson et al., 2005a; Edvinsson, 2004; Doods et al., 2000; Kapoor et al., 2000).

Data from recently published clinical proof-of-concept study by Olesen et al. (2004) demonstrated the effectiveness and safety of olcegepant for acute treatment of migraine, in which the response rate was found similar to oral triptans. No cardiovascular side effects have been reported following administration of olcegepant. The lack of cardiovascular side effects may prove to be a major advantage for using CGRP receptor antagonists to treat migraine (Durham, 2004b).

6.2. Anticonvulsants

Migraine and epilepsy share several features and respond to many of the same pharmacological agents suggesting similar mechanism may be involved in their pathophysiology, hence new targets are being investigated for the prophylactic therapy of migraine (Cutrer, 2001). Amongst these, anticonvulsants as a class of drugs hold promise for the migraine prophylaxis (Table 6). These drugs are thought to act through multiple mechanisms involving voltage gated ion channels, ligand gated ion channels, GABA (γ-amino butyric acid), glutamate etc. In the central nervous system, GABA is a major inhibitory neurotransmitter and known anticonvulsant drugs like sodium valproate, topiramate and gabapentine have been shown to be effective in preventing migraine through modulation of GABA neurotransmission (Cutrer, 2001; Hering and Kintzky, 1992; Magnus, 1999).

6.3. Histamine H₃ agonists

In recent study, histamine H₃ agonists are evaluated for the safety and efficacy for migraine prophylaxis. Milan-Guerrero et al. (2003) in the first part of their study determined the undesirable symptomatic effects of N-alpha-methylhistamine, a H₃ receptor agonist in healthy human volunteers and failed to identify adverse effects and in their second part of their study N-alpha-methyl histamine, at doses 1 and 3 µg was found to be significantly reduced the frequency, intensity and duration of migraine attacks as well as the need to rescue analgesics in 18 patients. Hence carefully controlled doses of H₃ receptor agonist may offer an alternative approach to migraine prophylaxis.

6.4. Botulinium toxin type A

BoNT-A, produced by the bacterium Clostridium botulinum consists of a heavy chain and light chain linked by a disulfide bond. BoNT-A binds to pre-synaptic nerve terminal

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**Table 6**

<table>
<thead>
<tr>
<th>Preventive drugs</th>
<th>Contraindications</th>
<th>Indication</th>
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<tbody>
<tr>
<td>β blockers</td>
<td>Asthma, depression, congestive heart failure, Raynaud’s disease, diabetes</td>
<td>Hypertension, angina</td>
</tr>
<tr>
<td>Antiserotonin – Pizotifen, methysergide</td>
<td>Obesity, peripheral vascular disease</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Ca²⁺-channel blockers-Verapamil</td>
<td>Constipation, hypotension</td>
<td>Migraine with aura, hypertension, angina, asthma</td>
</tr>
<tr>
<td>Flunarizine</td>
<td>Parkinson’s disease</td>
<td>Hypertension, familial hemiplegic migraine</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Mania, urinary retention, heart block</td>
<td>Other pain disorders, depression, anxiety disorders, insomnia</td>
</tr>
<tr>
<td>Serotonin specific reuptake inhibitor</td>
<td>Mania</td>
<td>Depression, obsessive compulsive disorder</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>Glaucoma, urinary retention</td>
<td>Refractory depression</td>
</tr>
<tr>
<td>Divalproex/valproate</td>
<td>Liver diseases, bleeding disorders</td>
<td>Mania, epilepsy, anxiety disorders</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Liver diseases, bleeding disorders</td>
<td>Mania, epilepsy, anxiety disorders</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Kidney stones</td>
<td>Mania, epilepsy, anxiety disorders</td>
</tr>
<tr>
<td>NSAIDS (Naproxen)</td>
<td>Ulcer disease, gastritis</td>
<td>Arthritis, other pain disorders</td>
</tr>
</tbody>
</table>
and is internalized into the cell, where it inhibits acetylcholine release by interfering with vesicle docking. These effects make BoNT-A useful for the treatment of many disorders related to excessive muscle contraction, such as strabismus, blepharospasm, hemifacial spasm and cervical dystonia (Mahant et al., 2000). New applications of BoNT-A in pain therapy support a mechanism for pain reduction that is more complex than a simple secondary effect of muscle relaxation. BoNT-A has been used successfully to treat several different types of headaches, including tension type headaches (Schulte-Mattler et al., 1999), cervicogenic headaches (Freund and Schwartz, 2000) and migraine (Brin et al., 2000). Although some types of headaches may have been relieved by the inhibition of muscle contraction at trigger points, the efficacy of BoNT-A in treating migraine headache implies a direct action on sensory neurons, with an indirect central action. It is believed that release of vasoactive neuropeptides, such as SP and CGRP from the trigeminal nerve onto the vasculature produces vasodilatation and plasma protein extravasation due to increased permeability of post capillary venules (Table 7). It is proposed that, the effectiveness of BoNT-A for the treatment of migraine in the clinical setting may be due to its inhibition of neurogenic inflammation induced by the peripheral release of SP and CGRP (Cui et al., 2004).

6.5. Coenzyme Q10

There has been recent interest in the role that mitochondria may play in migraine pathogenesis. It is clear from the recent studies that at least a subset of migraineurs has a dysfunction in mitochondrial energy metabolism. Coenzyme Q10 is an essential element of the mitochondrial electron transport chain. It is naturally occurring, small hydrophobic substance that freely moves throughout the membrane transferring electrons from the NADH dehydrogenase complex and the succinate-Q-reductase complex to cytochrome C. In addition to its actions as an electron carrier, coenzyme Q10 may act as antioxidant and help protect the myocardium from post-ischaemic reperfusion injury (Frei et al., 1990; Ohhara et al., 1981). If mitochondrial dysfunction is playing a role in migraine genesis then coenzyme Q10 could improve mitochondrial function and thus prevent migraine headaches. This belief is not without precedence as riboflavin, in an open label study (Schoenen et al., 1994) and a placebo-controlled trial (Schoenen and Jacquy, 1998) has been shown to reduce migraine frequency. Riboflavin is indirectly involved in the electron transport chain as a precursor of flavin mononucleotides. Coenzyme Q10 is an essential element of the electron transport chain, suggesting that it could also work as migraine preventive (Rozen et al., 2002).

6.6. NK-1 receptors

According to neurogenic inflammation theory of migraine, SP induces dural inflammation and increases sensitization to migraine headache pain by stimulating NK-1 receptors (Moskowitz et al., 1987). Lanepitant is a high affinity, non-peptide, competitive NK-1 receptor antagonist that acts both peripherally and centrally and reported to be effective in guinea pig model of dural inflammation (Goldstein et al., 1999). Thus, NK-1 receptor antagonists may have a role in migraine therapy.

6.7. Nociceptin

Nociceptin is an endogenous ligand for the opiate-4 (OP-4) receptor. The OP-4 receptor abundantly expressed in various CNS structures in rodents, nonhuman primates and in humans, supporting the role of nociceptin in multitude of CNS functions, including motor and balance control, reinforcement and reward, nociception, the stress response, sexual behavior, aggression and autonomic control of physiologic processes (Moran et al., 2000). It has been reported that approximately 70% of neurons in the human trigeminal ganglion exhibit nociceptin immunoreactivity and express OP-4 receptor mRNA. In these cells nociceptin is co-localized with CGRP and substance P, marker peptides of the trigeminovascular system. This distribution suggests that nociceptin may be involved in the regulation of neuropeptide release from trigeminal nerve terminals and perhaps in migraine (Hou et al., 2003). Interestingly, in an animal model nociceptin dose-dependently suppressed the neurogenic dural vasodilatation, while it had no effect on baseline vessel diameter (Bartsch et al., 2002), also in a recent study lower circulating levels of nociceptin was observed during migraine attacks (Ertsey et al., 2004, 2005). Hence drugs targeting OP-4 receptor might be a promising alternative in the pharmacological treatment of migraine.

6.8. Melatonin

Melatonin is a derivative of essential amino acid tryptophan, synthesized in the pineal gland. It has wide therapeutic implications including sleeping disorders, circadian rhythm, insomnia in blind people, insomnia in elderly patients, aging and Alzheimer disease (Bubenik et al., 1998). It has been observed that some patients reporting

<table>
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<th>Table 7</th>
<th>Characteristics of serotonergic receptors involved in migraine</th>
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<tr>
<td>Receptor</td>
<td>Effector</td>
</tr>
<tr>
<td>5-HT_{1B}</td>
<td>↓ Adeny1 cyclase</td>
</tr>
<tr>
<td>5-HT_{1D}</td>
<td>↓ Adeny1 cyclase</td>
</tr>
<tr>
<td>5-HT_{1F}</td>
<td>↑PLC</td>
</tr>
<tr>
<td>5-HT_{2B}</td>
<td>↑PLC</td>
</tr>
<tr>
<td>5-HT_{7}</td>
<td>↑Adeny1 cyclase</td>
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*Selective 5-HT_{1B/1D} receptor antagonist.
their headaches predominantly or specifically at a certain period of the day. Both episodic and chronic migraineurs reported waking up in the morning with headaches or being woken up at night by the headache (Paiva et al., 1995). Also migraine patients without depression had lower levels of melatonin than controls. Since, melatonin is involved in cerebrovascular regulation, treatment of headache disorders including migraine is promising. Melatonin may also be involved in migraine comorbidity. Insomnia in headache patients is the most likely associated condition in migraine to respond to melatonin therapy (Peres, 2005). However, the data from large human trials are yet come to provide a proof-of-concept for the potential role of melatonin therapy in migraine.

7. Concluding remarks

Now the migraine research is beginning to be focused on the development of novel agents for the acute/prophylactic treatment like CGRP receptor antagonists, nociceptin and melatonin. Thus, there is a rationale to believe that the new class of emerging therapies will provide further information on the better understanding of molecular pathophysiology of migraine.

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