Histamine in Migraine and Brain

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Background.—Histamine has been studied in both health and disease since the initial description a century ago. With its vasodilative effect, it was suggested early on to be involved in the pathophysiology of migraine. Over the past 25 years, much has been learned about histamine as a neurotransmitter in the central nervous system. The role of this neurotransmitter system in migraine has not been previously reviewed.

Objective.—Discuss a potential role of the brain histaminergic system in migraine.

Methods.—Unstructured literature search with a no specific hypothesis-driven approach.

Results.—There is substantial evidence that systemically given histamine may elicit, maintain, and aggravate headache. The mechanisms for this are not known, and histamines do not penetrate the blood–brain barrier (BBB). However, circulating histamine may influence hypothalamic activity via the circumventricular organs that lack BBB. In the rat, prolonged activation of meningeal nociceptors induced by dural mast cell degranulation has been observed. Subcutaneous injections of N-alpha-methyl histamine, a catabolite of histamine with high affinity to the histamine H3 receptor, probably have some migraine preventive effect. A negative feedback on histamine release from mast cells in proximity to C-fiber endings has been a postulated mechanism.

Most antihistamines have shown to be ineffective as acute medication for migraine. Two centrally acting potent H1 receptor antagonists (cinnarizine and cyproheptadine) have been reported to be efficacious in preventing migraine. However, the proof for this is limited, and their efficacy has been ascribed other actions than the antihistaminergic. In general, lack of specificity and side effects limit the potential use of centrally acting H1 and H2 antagonists.

Brain histamine is synthesized by neurons that are restricted to the posterior basal hypothalamus, more specific to the tuberomamillary nucleus (TMN), and that project practically to the whole central nervous system. The posterior hypothalamus is a suspected locus in quo in several primary headaches. Recently, a positron emission tomography study performed in the prodromal phase of migraine attacks supported the idea of initial involvement of this area. In another recent study, the thalamic nuclei receiving trigeminal output was also shown to have direct connections with the ventral TMN. The central histaminergic system plays an important role in the complex sleep–wake cycle, promoting cortical excitability during wakening and attention, and it consolidates the wake state. The period of the day, in the evenings and during the night, when there is reduced susceptibility for migraine attacks corresponds with less central histaminergic firing. Activation of both the H3 and the H4 receptor promotes inhibitory actions on neurons. The H3 receptor causes autoinhibition of the histaminergic neurons themselves, and centrally acting H3 receptor agonist prodrugs have shown to both inhibit neurogenic inflammation in dura, to induce sleep, and to produce antinociception. There are no registered ongoing studies on H3 and H4 receptor ligands in migraine.

Conclusion.—The role of the central histaminergic system in migraine is largely unexplored, but findings from preclinical research may be linked to several aspects of the disorder. The histaminergic system of the brain may play an important role, especially in the initial phase of an attack, and histamine H3 and H4 receptor ligands may potentially have migraine prophylactic properties. However, the basis for this is still circumstantial, and the evidence is lacking.

Key words: histamine, migraine, hypothalamus, pathophysiology, antihistamine, chronobiology

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Migraine is clinically a well-described entity, essentially a disorder with episodic manifestations of head pain associated with a hypersensitive sensory apparatus (photophobia, phonophobia, nausea, and vomiting), what may be considered a “noise phenomenon.” The ability to habituation, what enables people to operate in an otherwise noisy environment, seems to be reduced in migraineurs, even between attacks. However, there is a great leap from describing the phenomenology to understanding the biology of migraine, but in recent years, a few major steps have been taken. There is now a rather comprehensive understanding of the neurobiology of the aura, being caused by a neurophysiological phenomenon called cortical spreading depression (CSD), and the pain caused by activation of trigeminal fibers innervating the dura and the cranial vessels (collectively called the trigeminovascular system). The triggering and ending mechanisms of attacks remain largely enigmatic. A temporary loss of balance between excitatory and inhibitory processes seems to spring up, and this may theoretically occur on both a cellular, synaptic, and network level. From the classic view that migraine attacks originate in structures outside the brain, that is by activation of afferent nociceptors in cranial vasculature, there has been a shift toward a central theory where intrinsic brain activity drives the initial symptomatology (prodromal symptoms and aura) and triggers a sterile meningeal inflammation that causes pain, but this is still a matter of controversy. Amines, especially serotonin with its vasoconstrictive and migraine-pain reducing properties, have for a long time been implicated in the pathophysiology. Histamine, a monoamine most often linked to gastric secretion, mast cells and the immune system, is also a neurotransmitter in the central nervous system, and has been implicated in many brain diseases, including migraine and other pain conditions. It is well known that histamine can cause both recurrence of a drug eliminated headache, exaggerate a unilateral pre-existing headache, and trigger both an immediate and delayed headache. Histamine essentially does not penetrate the blood–brain barrier (BBB), and these effects have been ascribed peripheral mechanisms. The involvement of mast cells has gained some attention over several decades, initially as a source of vasodilator substances and in view of migraine as an allergic disease, but later, more specific as an activator of a pain pathway underlying migraine headache. Neuronal histamine has gained rather scantly attention in migraine research, and with the growing knowledge of the central histaminergic system and indirect evidence for an important role of the hypothalamus in migraine pathophysiology, a review with future perspectives of the role of brain histamine is considered highly valuable.

HYPOTHALAMUS A LOCUS IN QUO?

An important role of hypothalamus in migraine pathophysiology has been suggested for many years, and a large body of indirect evidence for this has accumulated. Premonitory symptoms, that most often indicate change in arousal, implicates an early involvement. Burstein and Jakubowski have put forward a hypothesis that explains how migraine triggers may activate hypothalamic, limbic, and cortical regions through a common pathway. Until recently, tangible evidence for hypothalamic activation during migraine was lacking, but in 2009 it was demonstrated on positron emission tomography (PET) scanning during spontaneous attacks. To demonstrate that such activation is not driven by pain, PET scanning during the prodromal phase of migraine was suggested, and such a study with positive result was recently performed. The migraine attacks were triggered by intravenous nitroglycerin. How certain drugs and changes in homeostasis may trigger migraine is unknown. It has been shown that systematically administered nitroglycerin may increase nitric oxide (NO) release in the posterior hypothalamus and may potentially modulate the release of histamine. The study should be reproduced by using other triggers, including histamine. To speculate further, small brain structures that lack BBB, the sensory circumventricular organs (CVOs), may provide the answer. These structures are located around the third and fourth ventricles, are highly vascularized, and are exposed to a wide range of signals from the blood. It was shown early on that the CVOs of the rat can take up biogenic amines from the circulation, but the significance of this in humans is not
known. However, there is no doubt that the CVOs constitute integral components of central nervous system circuits and are crucial for maintaining many homeostatic functions. In a study of mice that are genetically unable to make histamine (histidine decarboxylase deficient mice) where acute pain was induced by a single subcutaneous injection of formalin, highly activated c-fos expressions were observed in the circumventricular organs. This was not observed in wild-type control mice, indicating that histamine at least is involved in both the pain response and the regulation of the brain–blood–cerebrospinal fluid interface. Through interconnections with several nuclei of the hypothalamus (and the brain stem), central nervous influence may be exerted, and migraine may possibly be triggered.

The increased metabolism seen in the PET study from 2009 was more anterior in the hypothalamus than previously described in trigemino-autonomic cephalalgias. Notably, the resolution of PET imaging is not large enough to localize the exact structure involved, and sometimes not even the side. However, cluster headache with its sleep-related alarm clock regularity, and migraine with its stress-related association and remission with sleep, indicate that different mechanisms, and perhaps different parts of hypothalamus, may be involved in the pathophysiology. Since a major role of the central histaminergic system, with all its neurons localized to the posterior part of hypothalamus, seems to be the maintenance of wakefulness during environmentally imposed challenges, one may also speculate if aberrational histaminergic firing causes the susceptibility to attacks.

LOCATION OF HISTAMINE IN THE BRAIN AND ITS ASSOCIATION TO MIGRAINE

Histamine, chemically with an imidazole ring, and ethylamine as a ground structure shared with dopamine, norepinephrine and serotonin, is synthesized in several types of cells of neuroepithelial and hematopoietic origin, and has a wide range of functions outside the nervous system. From blood histamine enters the brain poorly, but mast cells, which are resident in peripheral tissues and contribute to pain in many experimental inflammatory pain states, can rapidly penetrate the BBB, particularly under pathological conditions, and be a substantial source. Noteworthy, the ependymal cells of the brain and cerebrovascular endothelial cells may also produce histamine. At least they express the histamine-synthesizing enzyme histidine decarboxylase (HDC) in rodents.

Mast Cells.—Mast cells may be found in the dura mater in close proximity to trigeminal nociceptive afferents. Through a series of studies by Moskowitz and coworkers, migraine has been attributed to a local sterile meningeal inflammation, and histamine may play an important role in this. Experimental animal studies have shown that mast cells may degranulate as a response to activation of meningeal nociceptors, and this response is associated with reinforced and prolonged activation of the trigeminal system. The accumulation and degranulation of mast cells, and the following nociceptive sensitization, may be mediated by substance P (SP) via NK1 receptor. However, no elevation of SP has been shown in migraine. Neither have antagonists of SP, which can completely block neurogenic inflammation in humans, proven effective in the acute treatment of migraine, nor poor CNS penetrating or more lipophilic compounds. Notably, Clarke and coworkers found that a low level of SP in the CSF increased the risk of developing post-lumbar headache, and postulated a premorbid upregulation of NK1 receptor as explanation. If activation of plasma cells with upregulated receptors occurs early in a migraine attack, substance P-levels during the headache may not necessarily be elevated compared to controls, and since degranulation of mast cells already has occurred in the pain phase no effect of blocking NK1 receptor can be expected. Reproducing the findings and testing the hypothesis of Clarke et al may thus be important for a further understanding of predisposing factors of headache attacks in general. Increased levels of histamine in both plasma and CSF during migraine attacks have been reported but should be confirmed in newer studies. Another vasoactive peptide with much the same properties as SP, calcitonin gene-related peptide (CGRP), has been documented in increased levels in plasma during migraine, and has been shown to be an effective target of attack treatment. Both SP and CGRP, released from activated
meningeal receptors, may induce degranulation of resident dural mast cells, and increased levels of histamine during pain may thus be a secondary phenomenon. In an experimental rat study, histamine produced direct vasodilatation in the dura and activated meningeal afferents (without releasing CGRP), and the increase in meningeal blood flow remained unchanged during both during CGRP, NO synthesis and H₃ blockade.

The Brain Histaminergic Neurons.—The neurons that synthesize histamine, estimated to constitute at least 64,000, are restricted to the posterior basal hypothalamus, in the tuberomamillary nucleus (TMN). The histaminergic neurons are found between the mammillary nucleus and the optic chiasma at the tuber cinereum. The TMN is rather precise morphologically defined but has extremely irregular cell borders, and it is important to remember that short association fibers abound, that there are extensively crossing of histaminergic fibers, and that there seems to be little topological organization. Further, similar to other biogenic amines, most histaminergic endings (varicosities) do not make close contact with postsynaptic sites. Histaminergic varicosities also appear to make contact with blood vessels and glia, and some of the ventrally located cells may also make direct contact with the cerebrospinal fluid. The TMN receive afferents from other hypothalamic areas, especially orexinergic, and from other areas, including noradrenergic (A1–A2) and serotonergic (B5–B9). These have all been incriminated in migraine pathophysiology, but their role is far from clear. Still, the serotonin receptor (5-HT₁) agonists are the best available acute treatment for migraine. Most interesting, there seems to be convergent excitation of dorsal raphe serotonin neurons by the orexinergic, histaminergic, and noradrenergic systems, and a modulating role of all these systems is plausible. Primarily acting as a local hormone with widespread neuronal effects, and with the possibility to regulate blood vessel tone and glial activity, the histaminergic system as a whole has been attributed a wide range of coarse-modulating functions. Recent research, however, also indicate functional distinct circuits with more selective response and more discrete effects. Heterogeneity of histamine neurons in response to stress has been well documented. In rodents, stress-sensitive histamine neurons are mainly found in the rostral clusters (E4–E5). In general, histamine release is a sensitive indicator of stress. Thus, the firing during waking is variable. During drowsiness and sleep, however, the firing from the histaminergic neurons are absent, reportedly the most wake-selective firing pattern identified to date. Gamma-aminobutyric acid release, from neurons in the anterior hypothalamus (ventrolateral preoptic nucleus), in the posterior hypothalamus, directly silences the histaminergic neurons during sleep. Electrical stimulation in the same/adjacent area may also reduce pain response and reduce headache attack frequencies. In a recent study projections from TMN to thalamic trigeminovascular neurons were demonstrated in the rat, implicating that central acting histamine may play a role in triggering attacks, “by disrupted sleep, skipping meals and emotional reactions” as expressed by the authors.

The Posterior Hypothalamic Area.—The posterior hypothalamic area (or nucleus) is the region above the mamillary bodies at the side of the third ventricle, consisting of large neurons that do not contain histamine, and is a well-known target for deep brain stimulation (DBS) in primary headaches, especially cluster headache. The mechanisms for actions are not understood. Fontaine et al scrutinized the anatomical location of stimulating electrodes in 10 patients of whom 5 had responded to the DBS, and found that in all responders the electrodes were located posterior to the hypothalamus (posterior to mamillary body and the mamillo-thalamic tract). As mentioned above, the well-defined boundary of hypothalamic nuclei is somewhat artificial, and posterior border region merges caudally with the mesencephalic reticular formation. According to Fontaine and his colleagues, the electrodes were still a few millimeters anterior to the periaqueductal grey matter (PAG), a well-known target for alleviating chronic pain in general and a structure strongly implicated in migraine pathophysiology. Besides via the PAG, the hypothalamus may contribute to modulation of pain via several connections to brain stem areas involved in pain processing, such as the nucleus tractus solitaries, rostral ventromedial medulla, nucleus raphe
magnus, and the trigeminocevical complex. Through the trigeminohypothalamic tract and via the trigeminal autonomic reflex, the hypothalamus is able to modulate both the pain, changes in cranial vasculature and parasympathetic symptoms observed during migraine. As mentioned above, TMN projections are also likely involved through modulating thalamocortical neuronal circuits. If we stick to the idea that hypothalamus is involved early in an attack, in the premonitory phase, and that an increased neuronal excitability is a fundamental migraine property, reducing histamine firing (and stress) could potentially lower the susceptibility of attacks.

PROPERTIES OF THE HISTAMINERGIC NEURONS AND THE TEMPORAL PATTERNS OF MIGRAINE

Migraine attacks do actually not occur at random times. A clearly reduced attack frequency in the evenings and during the night (Figure), in the time period where the natural “clock hormone” melatonin normally is excreted, is well documented. However, melatonin has not proven to be an efficacious prophylactic remedy. While sleep, a well-known terminator of migraine, seems to protect against attacks, the transition from sleep to awakening seems to be a vulnerable time with attacks more likely to occur. Both lack and too much sleep are important migraine triggers. The susceptibility of attacks is obviously also high during normal work hours, consistent with stress being the most frequent reported migraine trigger. Based on these observations, the increased susceptibility to migraine attacks may reflect increased or relatively sudden changes in central histaminergic firing, for instance in the early morning migraine. As mentioned in the previous section, the histaminergic system represents a major waking system. The neuron firing is high during waking or attention compared to sleep, with increased release of histamine in the prefrontal cortex and the anterior hypothalamus. Mice unable to synthesize histamine (histidine decarboxylase-KO mice) show permanent changes in cortical electroencephalography and sleep–wake cycle, and no increase in arousal when placed in a novel environment. Histamine probably plays an important role in wake consolidation. In a primate model, with wake-consolidated squirrel monkeys, studies have shown that CSF histamine has a robust daily rhythm, not significantly affected by locomotion or the use of γ-hydroxybutyrate and modafenil. However, sleep deprivation increased the concentration of histamine in the CSF. A robust relationship between sleep disturbances and migraine is documented in the literature, but the underlying mechanisms are not known. A direct consequence of insomnia may be increased cortical excitability in a brain that is supposed to rest. Increased cortical excitability has been postulated as a basic phenomenon of the migrainous brain, and is tightly associated to increased susceptibility to cortical spreading depression. Much data support that the first phase of a migraine attack resides in the cortex, but clear demonstration of this is lacking. A few studies support the idea that poor sleep per se is causing susceptibility of attacks. In a prospective recording of almost 2000 migraine attacks,
those related to insomnia had preponderance in the morning hours. The majority of subjects experiencing insomnia-related attacks were awake when it occurred (88%). By using actigraphy, Bruni et al found decreased physical activity and difficulty initiating sleep prior to attacks. Further, polysomnographic studies have also shown reduced sleep quality in migraineurs compared to healthy controls.

The human sleep–wake cycle is complex, regulated by multiple genes and environmental factors. The temporal patterns of migraine, associated to migraine aura and insomnia, strongly indicate that the circadian system, with its rhythms driven by the suprachiasmatic nucleus (SCN), contributes to regulate the susceptibility of attacks. A direct circadian misalignment, leading to both increased sleep disturbances and susceptibility to attacks, cannot be ruled out. A possible genetic link between circadian regulation, cortical excitability, cortical spreading depression and migraine, was found in 2005. Researchers were then able to identify a gene mutation (T44A) that was responsible for advanced sleep phase syndrome in a family, causing the family members to operate a shortened internal clock. The five-family members also suffered from migraine with aura. Later, T44A CK1δ mice have been claimed to display several traits consistent with migraine, including a hyperexcitable cortex with respect to CSD and a lowered threshold for allodynia. Based on recent studies on a murine model of hemiplegic migraine (mice carrying mutated Ca,2.1 calcium channels), abrupt circadian rhythm changes have been postulated as a migraine trigger due to inadequate adaption mechanisms. These experimental studies suggest that circadian dysregulation may be a common feature of migraine. Histamine modulates circadian rhythms, and phase-shift them in a manner similar to light. Some even consider histamine to be the final neurotransmitter in the entrainment of the superior biological clock, the SCN of the anterior hypothalamus. From clinical practice, maintaining a normal diurnal rhythm seems to be essential for good migraine control. Studies documenting this are, however, absent. The effect of shift work on migraine is also largely unknown. It is a clinical experience that patients who are severely affected by migraine tend to avoid working night shift. This seems rational based on studies that have shown that shift workers do not adapt new circadian rhythms. Stabilizing the sleep–wake cycle with melatonin did not seem to affect the frequency of migraine attacks, but could antihistamines be effective?

**THE HISTAMINE DYNAMICS, RECEPTORS, AND ANTIHISTAMINES IN MIGRAINE**

Histamine has been extensively studied since it was isolated from the mould ergot a century ago. It is synthesized from the amino acid L-histidine in one step by the enzyme L-HDC. Large systemic doses of L-histidine will raise the brain histamine concentration, but whether it triggers migraine is unknown. In the brain, histamine is almost exclusively metabolized by methylation, in the first hand carried out by the enzyme N-methyltransferase (HMT) producing N-methylhistamine. A polymorphism in the human HMT (Thr105Ile) is associated with decreased enzyme activity and presumed increased brain histamine levels. No increased prevalence of this gene variant was found in a study of migraine. Systemically, histamine is metabolized by oxidation carried out by diamine oxidase (DAO). DAO is probably not constitutively expressed in the mammalian brain, but small amounts are detectable. In the 1970s, Sjaastad and colleagues studied extensively the total turnover of histamine by assessing histamine and its catabolites in urine and whole blood of both migraineurs and patients with cluster headache. The findings are difficult to interpret but, in short, a minor increase in turnover was found in cluster headache but not in migraine. However, the mean excretion of histamine in the urine was lower during attacks than during attack-free periods.

Histamine acts through four metabotropic histamine receptors which are all G-protein-coupled (GPCR); H₁R–H₄R is pharmacologically active in only seconds, and the endogenous ligand has relatively low affinity to H₁ and H₂ receptors compared with the H₃ and H₄ receptors. Some H₂ receptor agonists and H₁ ligands are also potent ligands for H₄ receptor, but in general the antihistamines currently in clinical use (more than 45 H₁ antihistamines are available) have probably little or no affinity for H₄R and H₃R.
**H₁ Receptors.**—H₁Rs are widely distributed in the body, including the brain. Activation in the brain induces depolarizing responses in many areas, and functions like arousal, regulation of the sleep–wake cycle, memory and cognition are mainly mediated by this receptor. Studies where ³H-pyrilamine (mepyramine) binding has been used to indicate, however, that a major portion of H₁R actually may be associated with non-neuronal elements such as vessels and glia. Histamine may for example serve as a signal for supply of more glucose from capillaries to astrocytes in the setting of increased synaptic activity. It has been known for a long time that histamine may induce headache, and that both the blocking agent mepyramine and cimetidine (H₂-blocker) may reduce and abolish histamine induced headache. When H₁R is stimulated in cranial arterial endothelium, nitric oxide synthase is activated with subsequent formation of NO and dilatation of the vessel. In the mid-1990s, Olesen and colleagues formulated the “NO-hypothesis” as an explanation of why migraine is triggered; the primary event is a vasodilatation causing the throbbing headache. They further assumed that the triggering mechanisms were mediated via the vascular H₁ receptor. However, a disturbing fact remained; neither H₁- nor H₂-antihistamines had shown to be effective in treating migraine, and the vascular changes in migraine are in many opinions a secondary response to neuronal activation. The lack of effect of antihistamines must be interpreted with caution. If migraine pain results from binding to its receptors, one cannot expect an event that already has occurred to be blocked. Most of these old antihistamines are lipophilic compounds that readily penetrate into the brain, and clearly cause both anti-nausea and sedative effects. H₁-receptor antagonists may therefore work well in treating associated symptoms of migraine, like nausea and vomiting, but also potentially damp cortical excitability. They are widely used in pregnant and pediatric patients, and sometimes in combination with analgesics. Actually, two antihistamines (cinnarizine and cyproheptadine) that cross the BBB and cause sedation have been reported to be efficacious in preventing migraine. Their efficacy has been ascribed by other actions than the antihistaminergic. Interestingly, meclizine, an antihistamine with a chemical structure similar to cinnarizine but with no effect on calcium channels, has not been rigorously tested in migraine, but favorable effects were reported in a case report in the 1950s. To the best of our knowledge, no randomized controlled trial with first-generation H₁-antihistamines in migraineurs with comorbid insomnia has been performed. More than 70% of CNS H₁Rs are typically occupied after standard doses, and side effects limit their potential use.

Alteration of brain histamine levels has also been shown to influence nociception in general, and both the H₁ and H₂ receptors are probably involved. As acute medication for migraine, antihistamines have been studied as analgesia potentiators with mostly negative results. In one study, the H₂-antagonist hydroxyzine was compared to placebo. No effect was seen in migraine without aura, but a possible pain-relieving effect was suggested by the data in migraine with aura.

**H₂ Receptors.**—Like H₁R, H₂ receptors are postsynaptic and potentiate excitatory inputs or mediate excitatory actions on neurons. H₂R shows only about 40% homology with the H₁R, and much less is known of its effects in the CNS, partly because of limited available BBB penetrating H₂ receptor antagonists. Experimental studies have shown that short exposure of the H₂-agonist imipramine may cause enhanced firing of several types of neurons for hours. Such enhanced and long-lasting responses may be seen in cortical neurons in response to a sensory stimulus, possibly through depolarization that has decisive influence on the thalamic relay of sensory input. The prototypical H₂ antagonist cimetidine, developed to suppress stomach acid secretion has shown ineffective as prophylaxis for both migraine and cluster headache. Cimetidine, following systemic administration, only passes the BBB in very high doses, and only peripheral actions of H₂ antagonist have thus been evaluated in migraine.

**H₃ Receptors.**—Histamine has high affinity to the H₃R and exerts GPCR signaling, but spontaneous signaling can also occur in the absence of endogenous histamine or other agonist, so-called constitutive receptor activity. In contrast to the effects of H₁ and H₂ receptor activation, the H₃R, which is located pre-
synaptic both in the peripheral and central nervous system, shows low similarity to the H1R and H2R, and promotes inhibitory actions on neurons. H3R causes autoinhibition of the histaminergic neurons themselves. Several isoforms that might have different pharmacological profiles exists, and there is evidence for genetic polymorphism within the human H3R. One, where the amino acid 280 (alanine) is substituted to valine, the H3R_A280V variant, has been considered a risk factor for migraine. The authors of the study suggested that increase histamine release due to increased population of inactive autoreceptors may be the cause, and in a recent study it was shown that the A280V variant actually reduces the signaling efficacy of the H3R.

By modifying a side chain of the histamine imidazole molecule, selective and potent receptor agonists have been made, so-called (R)-α-methylhistamine compounds (RAMHs). Nα-methylhistamine is a histamine catabolite and an H3R agonist that is about 3 times more active than histamine. It was reported safe and effective as prophylaxis in 18 patients with migraine in an open clinical trial. Not surprisingly, the highest dose tested gave intense headache, probably due to the agonistic effect of H1 receptors. In a phase III study where 30 patients received Nα-methylhistamine subcutaneously twice a week for 12 weeks, the same research group found that it was superior to placebo. This H3 receptor agonist does not cross the BBB. Further, they showed that very low doses of histamine subcutaneous had effects similar to sodium valproate, topiramate, and botulinum toxin type A. The authors ascribed the efficacy to reduced neurogenic inflammation and activation of C-fiber endings through inhibition of mast cells. Again only peripheral mechanisms were evaluated. The idea of giving low dose histamine or its catabolite, is to stimulate the H3 – feedback loop and cause reduced histamine release. The findings in these studies are somewhat surprising, considering that peripheral-acting antihistamines do not prevent against migraine. Centrally acting H3R agonists may also have potential as migraine prophylactic drugs. The RAMH prodrug SCH50971 penetrates the BBB, and is reported to both inhibit neurogenic inflammation in dura mater and to induce sleep.

The RAMH immeepip given intrathecally produced maximal antinociception in wild-type mice but not in mice lacking H3 receptors. Both imidazole-containing and non-imidazole antagonists exist. These have been reviewed elsewhere, and are not considered useful against migraine.

**H1 Receptors.**—The H1 receptor, which shows considerable homology with the H3R (35%), is primarily localized in peripheral tissues and immune cells, including mast cells, but was recently detected in the human cortex and several subcortical structures. Its role in the CNS is largely unknown, but activation of H1R induces hyperpolarization in neurons of the mouse somatosensory cortex. As mentioned, cortical hyperexcitability, including the somatosensory cortex, appears to be a fundamental feature of the migrainous brain.

The similarities between H3R and H4R, with overlap in pharmacological profiles, have made preclinical data difficult to interpret but analogous to the potential cortical excitability reducing effect by activating the H3R, the same effect may perhaps be achieved by stimulating the H4R. In a recent study, intracerebroventricular administration of an H4R agonist in the mouse induced acute thermal antinociception. By using the H4 receptor antagonist JNJ-10191584, this effect was prevented. On the other hand, antinociceptive effect of a selective H4 receptor antagonist (JNJ-7777120) secondary to its anti-inflammatory actions has also been suggested. It is worth noticing that several neuroactive drugs, including amitryptiline which is an effective migraine prophylactic drug, bind to H4R.

**FUTURE PERSPECTIVES**

Alterations in the histaminergic system have been proposed in both neurological and psychiatric diseases, but to date, no specific disorder connected to a specific histaminergic dysfunction has been demonstrated. The role of peripheral acting histamine in migraine has been quite extensively explored, but its role as a potent modulator of meningeal nociceptors’ activity in migraine is far from clear. Activation of inhibitory H3 receptors has previously been suggested for migraine prophylaxis. Low doses of subcutaneous histamine may theoretically be sufficient to stimulate
sensitive H₃ receptors, activating a negative feedback on histamine release from mast cells in proximity to C-fibers. Actually, three Class II single-center studies (performed by the same research group), one with N-alpha-methyl histamine and two with histamine, have established subcutaneous histamines as probably effective for migraine prevention. However, its use is limited by an inconvenient treatment regime.

The role of the central histaminergic system in migraine is unexplored. At present, to predict the net effect of histamine in central networks seems quite impossible. However, both H₁R and H₄R ligands may theoretically have migraine prophylactic properties, but there seems to be a long and winding road before effective antihistaminergic treatment against migraine is established. Despite being promising drug targets for several diseases, the lack of specificity and undesired side effects will probably be a major problem. A search across electronic databases for ongoing studies on H₁ and H₄ receptor ligands in migraine or other types of headache was negative.

In general, incomplete understanding of the initial phase of the migraine attack is a major hindrance for the development of migraine prophylactic drugs. A deeper understanding of the chronobiology of migraine, the relationship to sleep and arousal, is needed. Preclinical studies exploring how hypothalamus may interact between the blood and brain to modulate thalamic and brain stem structures involved in migraine are probably the first key to unwind the etiology. This key may include histamine.

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Category 1

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