Nitric Oxide-Related Drug Targets in Headache

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Summary: Nitric oxide (NO) is a very important molecule in the regulation of cerebral and extra cerebral cranial blood flow and arterial diameters. It is also involved in nociceptive processing. Glyceryl trinitrate (GTN), a pro-drug for NO, causes headache in normal volunteers and a so-called delayed headache that fulfils criteria for migraine without aura in migraine sufferers. Blockade of nitric oxide synthases (NOS) by L-nitromonomethylarginine effectively treats attacks of migraine without aura. Similar results have been obtained for chronic the tension-type headache and cluster headache. Inhibition of the breakdown of cyclic guanylate phosphate (cGMP) also provokes migraine in sufferers, indicating that cGMP is the effector of NO-induced migraine. Similar evidence suggests an important role of NO in the tension-type headache and cluster headache.

These very strong data from human experimentation make it highly likely that antagonizing NO effects will be effective in the treatment of primary headaches. Nonselective NOS inhibitors are likely to have side effects whereas selective compounds are now in early clinical trials. Antagonizing the rate limiting cofactor tetrahydrobiopterin seems another very likely new treatment. It is more unlikely that antagonism of cGMP or its formation will be feasible, but augmenting its breakdown via phosphodiesterase activation is a possibility, as well as other ways of inhibiting the NO-cGMP pathway. **Key Words:** Cerebral circulation, drug development, experimental headache, headache, nitroglycerin, pain.

INTRODUCTION

Because it is generally accepted that there is no need for more triptans, future advances in migraine and other headaches must be based on novel targets. In this respect nitric oxide (NO) has been shown to play a significant role in migraine, tension-type headache (TTH), and cluster headache (CH). Indeed, not only can NO provoke an attack, but it seems to be involved for the entire duration of the attack.[1] Based on original work with glyceryl trinitrate (GTN), also called nitroglycerin, on the role of NO in migraine, we formulated the "NO hypothesis of migraine." The NO–cyclic guanylate phosphate (cGMP) cascade offers opportunities for pharmacological intervention, as activation of this pathway is present during migraine attacks and probably also in other primary headaches. Preliminary evidence indicates that inhibition of NO synthases (NOS) using L-nitromonomethylarginine (L-NMMA) is effective in the acute treatment of migraine attacks.[2] Because this avenue of novel drug development has not yet been pursued by pharmaceutical companies, it is considered timely to review the involvement of NO in the most important primary headaches, namely migraine, TTH, and CH.

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GENERAL ASPECTS OF NO

The general pharmacological aspects of NO have been described in numerous publications, which are probably well known to most readers of this journal.[3,4] Very briefly, NO is a gaseous signaling molecule that is present in most tissues throughout the body. It is formed by oxidation of L-arginine, resulting in the formation of NO and L-citrulline. This process is catalyzed by three different enzyme isoforms of NOS, namely endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS),[5] and involves several cofactors of which tetrahyrobiopterine is rate limiting in most systems.

NO has a free electron ($NO^{\cdot}$), but despite being a free radical, it is not toxic by itself. By reacting with superoxide, however, it forms peroxynitrite, which is a highly reactive free radical that exerts noxious effects on tissues. This mechanism is used in defense against infection when iNOS is activated and produces NO in high concentrations. Whether free radical formation plays a role at the lower concentrations seen in endothelium and neurons is uncertain.

Effect of NO in the cerebral and extracerebral circulations

The effect of NO in the cerebral circulation in health and disease has been extensively reviewed by Iadecola and Niwa.[6] In this respect, eNOS has been demonstrated in the endothelial cells of dural arteries, as well as cerebral arteries,[7,8] whereas nNOS is located in many central neurones, particularly moreso in the cerebellum than in the cortex. nNOS containing nerve fibers are in close contact with penetrating arterioles and may have a vasodilator effect. In the trigeminal ganglion, nNOS co-localizes with calcitonin gene-related peptide in a minority of neurones.[9] Interestingly, nNOS has also been located in perivascular nerve fibers on cerebral arteries from several species.[10,11] These peripheral nerves are nonadrenergic, noncholinergic, and have also been called nitrergic or nitroxidergic nerves.[12] These peripheral nerves have also been traced back to the spheno-palatine ganglion and belong to what has classically been regarded as the parasympathetic nervous system.[13] Although stimulation of these nerves potently dilates cerebral and extracerebral arteries, stimulation of the trigeminal ganglion in rats dilates blood vessels exclusively via liberation of calcitonin gene-related peptide.[9]

NO derived from GTN dilates cerebral and extracerebral arteries, but causes no change in brain blood flow in humans.[14] However, blockade of NO production with L-NMMA produced a dose-dependent increase in systemic blood pressure without changes of the velocity of blood in the middle cerebral artery or changes of the diameter of the radial artery.[15] Similarly, Lassen et al.[16] have reported that L-NMMA produced: 1) a 20% increase in blood pressure with a concomitant 24% decrease in heart rate at the maximal dose; 2) a 6.8% decrease in brain blood flow; and 3) no effect on acetazolamide-induced increase in cerebral blood flow. These results suggest that there is no basal NO tone in human cerebral arteries, but that there is a mild dilator tone in cerebral (and systemic) arterioles regulating blood flow and blood pressure.[16]

More marked effects of NO have been reported in animal experiments, possibly due to anesthesia and poor counter-regulatory mechanisms. Although this literature has been reviewed elsewhere,[6] it is noteworthy that NO seems to play a role in certain aspects of the regulation of brain blood flow. However, the effects of NO are often modest, and the literature is conflicting (e.g., see Fabricius and Lauritzen[17] and Fabricius et al.[18]).

Relatively little information is available concerning the effects of NO in the extracerebral and extracranial circulation. eNOS has been localized in the vascular endothelium of the rat dura mater[19,20] and GTN is a strong vasodilator in this preparation.[21] Moreover, NO in guinea-pig dura mater induces extravasation and other changes similar to those induced by neurogenic inflammation.[22] Interestingly, in humans, GTN has been reported to induce: 1) a much more pronounced dilatation in the superficial temporal artery than in the radial artery[23]; 2) a potent vasodilatation in veins throughout the body, including the head; 3) a marked increase in cerebral blood volume, probably because of cerebral venous dilatation[6]; and 4) no effect on regional cerebral blood flow.[14] Thus, the effect of GTN seems to be specific for arteries and veins, but it is not present in the arterioles that regulate tissue perfusion.

Effect of NO on nociceptive processing

NO seems to exert a modulatory role in the spinal trigeminal nucleus on the basis that: 1) NOS inhibition lowered activity of neurones with meningeal input in the rat spinal trigeminal nucleus[24]; and 2) c-fos expression in the trigeminocervical complex after stimulation of the superior saggital sinus was reduced by L-NAME[25]; 3) both NO and glutamatergic mechanisms augmented the response to noxious stimulation in studies of the first synapse in the trigeminal spinal nucleus[26]; 4) NO potentiated the response of trigeminal neurons to facial stimulation in the rat[27]; and 5) a biphasic response of trigeminal neurones after NO showed parallels to the biphasic response seen in migraine patients after GTN.[28]

PROVOKING HEADACHE WITH GTN

GTN is a lipid soluble substance that diffuses through all membranes, including the blood-brain barrier. In the tissues, it is chemically degraded and liberates NO like other nitrovasodilators[29]; thus, GTN is simply a carrier of NO to the tissues. Several tissues (particularly vascular smooth muscle) have the capability of converting GTN, and the availability of -SH groups is a limiting factor in this conversion. Indeed, as reported by Iversen,[23] N-acetyl cysteine: 1) delivers -SH groups and increases this conversion; and 2) potentiates the effect of GTN regarding both vascular responses and headache.[23]

Migraine

More than a century ago, it was known that nitroglycerin (GTN) could induce headache and that this headache was throbbing. Because migraine sufferers were more sensitive than nonmigraine sufferers, various attempts were made to use the response to GTN as a diagnostic test for migraine, but the overlap between migraine patients and normal subjects was too great with the transdermal application technique used. In older literature, no distinction was made between the immediate headache after administration of GTN and the headache that occurred in migraine patients long after the administration of GTN.[1,30] Sicuteri et al.[31] focused on this issue and suggested that migraine sufferers and first-degree relatives of migraine sufferers: 1) were more sensitive to

GTN than normal controls; and 2) developed a delayed headache that was migraine-like. Because of a lack of explicit diagnostic criteria for migraine at the time, it was not possible to analyze whether the headache did or did not fulfill diagnostic criteria for migraine.

A new era in the study of the GTN-induced headache occurred when Iversen et al.[32] used intravenous infusion of GTN to limit intersubject variability. For the first time, they also linked the effect of GTN to the liberation of NO. They evaluated the dose-response relationship between GTN and headache and also the within and between subject variability and found them to be excellent. The 10-min infusion period was too short. The 20-min infusion period has been used in subsequent studies. Isosorbide mononitrate (ISMN) delivers NO in a prolonged fashion and, correspondingly, the headache was also prolonged.[29] Similarly, the infusion of GTN for 7 h resulted in headache and dilatation of the radial artery lasting more than 7 h in normal volunteers.[33] Toward the end of the infusion, headache (in fact) increased and became migraine-like. These studies strongly suggest that NO is capable of inducing headache and of dilating extracranial arteries in normal volunteers. The induced headache was often pulsating, but usually did not have the associated symptoms of migraine.

In a study of 17 migraine patients (17 age- and sex-matched normal controls), as well as 9 patients with tension-type headaches, GTN was infused in increasing doses in a staircase design, which induced a dose-dependent headache in all groups.[34] In migraine sufferers, the headache was more severe, longer lasting, and did not return to baseline for the duration of the study, whereas this was the case in normal volunteers. Headache characteristics were scored according to ICHD-2 diagnostic criteria for migraine. The headache of migraine sufferers had more migraine characteristics than in the controls. After discharge, most patients developed an attack of headache fulfilling ICHD-2 diagnostic criteria for migraine without aura. Patients with TTH reacted midway between normal controls and migraine sufferers. In another double-blind, placebo-controlled crossover experiment, GTN (0.5 μg/kg/min) or the placebo was infused for 20 min in migraine without aura patients.[1] The experimental stress of the procedure did not induce migraine attacks because none developed migraine on the placebo. After GTN, 8 of 10 patients got a biphasic headache. The immediate headache that developed during GTN infusion had some migraine characteristics. The delayed headache in this study and in later studies had its maximum at approximately 7 h after the infusion, which fulfilled the diagnostic criteria for migraine without aura (FIG. 1). This experiment confirmed previous observations by Sicuteri et al.[31] that migraine sufferers have an immediate, as well as delayed headache, and that the latter, according to the patients, was indistinguishable

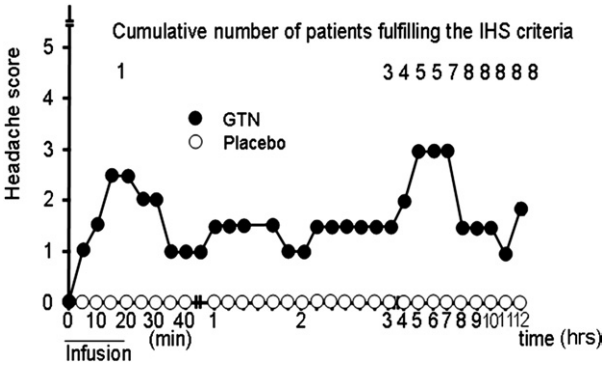

FIG. 1. A double-blind, randomized, placebo-controlled crossover experiment in which migraine patients received glyceryl trinitrate (GTN) 0.5 μg/kg/min for 20 min on one day and a placebo on another day. The headache was scored 0 to 10 on the y-axis. The GTN induced an immediate headache during infusion and a delayed headache 5 to 8 h after the infusion. The delayed headache was identical to the patients' usual migraine attacks. Formally the headache fulfilled diagnostic criteria for migraine without aura in 8 of 10 patients. (From Thomsen et al.,[68] with permission.)

from their spontaneous migraine attacks. The super sensitivity to GTN in migraine sufferers could be due either to the trait or state of migraine. In other words, it could depend on the migraine "make-up" or on the severity and frequency of attacks. In a double-blind, randomized, controlled study, patients with frequent attacks (≥12 attacks/year) were compared to patients with rare attacks (≤4 attacks/year).[34] Both groups developed a migraine attack without aura more frequently than previously seen in healthy subjects, and there was no statistical significant difference between the proportions of patients developing an attack in the group with frequent migraine *versus* the group with rare attacks.

All studies previously cited herein examined migraine without aura. Twelve sufferers of migraine with aura who never had attacks without aura were therefore compared to 14 healthy subjects.[35] Both groups received GTN (0.5 μm/kg/min for 20 min). Aura symptoms were not elicited in any subject, but have subsequently been observed by others in rare instances after GTN.[36] However, an attack fulfilling criteria for migraine without aura developed in 6 of 12 patients.[35] This was significantly more than in the normal controls in which no one developed a migraine attack. It was concluded that GTN can not induce an aura, but patients having migraine with aura are more prone to develop a migraine attack without aura than normal controls. However, the frequency of such attacks was less (50%) than in migraine sufferers without aura (80%). These proportions were based on small numbers, but subsequent studies have demonstrated almost identical figures in large numbers of patients.[36,37] The migraine aura is probably caused by a so-called cortical spreading depression,[38] which is a slowly spreading depolarization of all cellular elements

of the cerebral cortex; this phenomenon is associated with the production of NO. Indeed, the GTN experiments previously described herein suggest that the aura may produce headache via the production of NO. Thomsen[39] has extensively reviewed and summarized the early studies of GTN-induced headache.

Subsequently, Afridi et al.[36] performed a large study of GTN in migraine patients. They confirmed previous observations and also, for the first time, demonstrated premonitory symptoms just before GTN-induced migraine. Interestingly, in all these studies, GTN caused no pain other than headache, be it in normal volunteers or in migraine patients. Even peripheral pain thresholds have only been minimally altered by GTN[40] and central side effects (e.g., sedation, dizziness, etc.) have never been reported, suggesting a peripheral site of action of NO.

It is worthy of note that superoxide ($O2^-$) scavenges NO, and during hypoxia there is less superoxide available, and the same is true when hypoxia is caused by high altitude. Therefore, NO activity may be increased at a high altitude, which again is known to cause headache.[41] Indeed, L-arginine supplementation at a high altitude augmented the amount of exhaled NO and increased headache.[42] Seven healthy males participated in this double-blind crossover experiment. The increase in headache was significant in the treatment group at 12 h. Other studies have shown that the prevalence of migraine at a high altitude is significantly increased, even in natives to high altitude.[43] Continuous intake of GTN results in tolerance, an unwanted effect in cardiological therapeutic use, yet desirable when it comes to headache. In a randomized, double-blind, crossover design, 11 healthy subjects received 30 mg ISMN 3 times daily or a placebo for 7 days.[44] Wash-out between periods was 14 days or more. With this heavy dosing of an NO donor, 10 subjects fulfilled the pain subcriteria for migraine without aura, and 5 subjects fulfilled all diagnostic criteria for migraine without aura. This should be compared to the standard provocation with 20 min of intravenous infusion of GTN, which has rarely resulted in migraine headaches in normal volunteers. Therefore this study indicated that a high enough dose of GTN for a sufficiently long time can cause a migraine in half of all normal subjects. A close temporal relationship between the disappearance of headache and the disappearance of superficial temporal artery dilatation was observed. This occurred approximately after 72 h, whereas tolerance of the middle cerebral artery already occurred after 24 h. Therefore the study pointed to a possible extracranial site of action of NO. An increased sensitivity to GTN of migraine patients seems not just to relate to headache, because the dilatory response of the middle cerebral artery was greater in migraine sufferers than in normal controls.[45] This increase in the immediate vasodilator response may be accompanied by an increased vasodilator response during provoked migraine headache.[46]

The close temporal association between vasodilatation and headache caused by GNT does not necessarily reflect that headache is an effect of vasodilatation. In this respect, Thomsen et al.[40] studied nociceptive pain thresholds in humans during a GTN challenge. Pressure-pain detection and tolerance thresholds were determined by pressure algometry on a finger, in the temporal region with interposed myofacial tissue, and in the temporal region without interposed myofacial tissue. Relative to placebo, the three higher doses of GTN (0.25, 1.0, and 2.0 μg/kg/min for 20 min) induced a decrease in both detection and tolerance thresholds in the temporal region with interposed myofacial tissue. No such changes were observed in the other two stimulated regions. These results could perhaps reflect central facilitation of nociception by NO, but it seems unlikely that a central effect would be seen in only one of two studied temporal sites. Therefore, a peripheral site of action in myofacial tissue is more likely. The study has not been repeated, and the issue of central or peripheral sensitization caused by GTN is still open.

Histamine infusion has an effect similar to GTN.[47] It causes headache in normal volunteers and a more pronounced headache in migraine sufferers, plus a delayed headache fulfilling migraine criteria. Therefore it is reasonable to assume a final common pathway for histamine and NO-induced headache. However, H_1-receptor blockade did not prevent GTN-induced headache.[48] On this basis, histamine can be ruled out as a common mediator of NO- and histamine-induced headache.

NO has many different actions in addition to its activation of soluble guanylate cyclase, which leads to increased production of cGMP. The latter is broken down by phosphodiesterase 5, which again is inhibited by sildenafil. In two double-blind, randomized, crossover trials, sildenafil and placebo were compared in normal volunteers and in migraine patients. Sildenafil caused headache in the former and a migraine-like headache in the latter (FIG. 2).[49,50]

Tension-type headache

Olesen et al.[51] were the first to study GTN provocation in patients with TTH. In a controlled study, 17 patients with migraine without aura, 17 headache-free controls, and 9 patients with TTH all received a staircase infusion of GTN intravenously or a placebo. Because of the small size of the TTH group, no significant difference was observed from the placebo. Numerically, however, TTH patients got more headaches than the normal controls, but less than the migraine sufferers. However, the difference was not statistically significant, possibly because of the small sample size. No attempt was made to characterize the headache that TTH patients developed. Con-

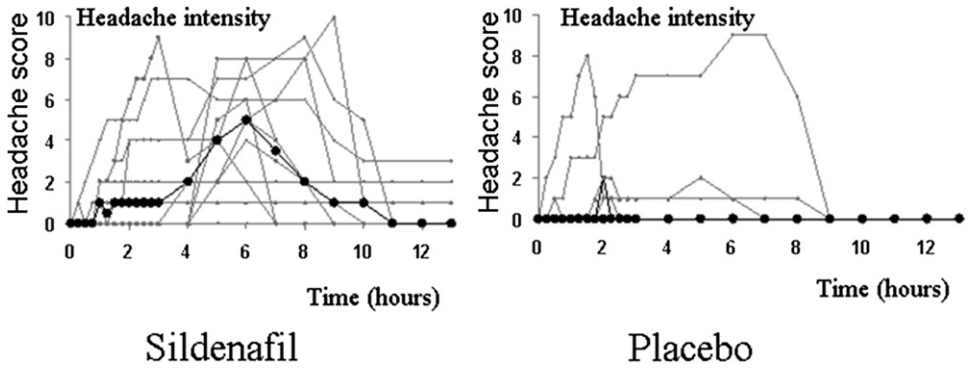

FIG. 2. The headache-induced effect of sildenafil, a phosphodiesterase 5 (PDE5) inhibitor, which inhibits the breakdown of cyclic guanylate phosphate, and hence causes its accumulation. The headache was scored on a 0 to 10 verbal rating scale. From 12 patients with migraine without aura, 10 developed a migraine attack after sildenafil and 2 after a placebo, which was a highly significant difference. Similar to provocation with glyceryl trinitrate (GTN), note that migraine attacks came after several hours, but unlike GTN there was no immediate headache after sildenafil, probably because it was given as a tablet. Another extraordinary finding was that cerebral arteries were not dilated, and cerebral blood flow did not increase after sildenafil. (From Kruuse et al.,[50] with permission.)

siderably more details were available in a double-blind, randomized, placebo-controlled, crossover study in which 16 patients with chronic TTH (i.e., TTH of 15 days per month or more) received GTN or a placebo.[52] Sixteen normal healthy controls also received GTN or a placebo in a double-blind, randomized placebo-controlled crossover fashion. The area under the pain curve was significantly greater in TTH patients than in normal controls, and peak headache was also significantly higher. Headache patients developed a delayed headache that peaked 8 h after an infusion of GTN and a smaller delayed peak headache was observed after a placebo. The placebo-induced delayed headache was considered to be a recurrence of the patients' spontaneous TTH. The delayed headache after GTN had the characteristics of TTH.

Thus, GTN induces an immediate headache, stronger than in healthy controls, as well as a delayed headache of the tension-type in chronic TTH patients. In the same experiment, muscle hardness, myofascial tenderness, and mechanical as well as heat pain thresholds were measured at baseline, and after 1 and 2 h. There was no difference between GTN and the placebo regarding muscle hardness, myofascial tenderness, pressure, or heat pain thresholds, neither in patients nor in the controls.[53] The unchanged sensitivity of pericranial myofascial pain pathways indicated that neither peripheral nor central sensitization was involved in the mechanisms of immediate GTN-induced headaches. No measurements were taken during delayed headaches in which sensitization is more likely to play a role. In the previously described experiments herein, blood was also drawn for analysis of arginine and citrulline. The former was unchanged in both patients and controls, whereas the plasma levels of citrulline increased significantly in patients 60 min after the start of GTN infusion.[54] No increase was observed in the controls. It was suggested that GTN infusion may trigger endogenous production of NO (as reflected in the side product citrulline) in patients with chronic TTH.

Cluster headache

Ekbom[55] examined the nitroglycerin test in the cluster headache. He described that cluster headache sufferers, while in a cluster period, always developed a cluster headache attack after a GTN challenge. He used sublingual GTN (1 mg), and the attacks usually occurred around 30 to 50 min after the challenge. The attacks were completely typical of the spontaneous attacks of the individual patient. A few weeks of therapeutic administration of long-acting organic nitrate for the treatment of angina may induce a cluster period in patients who had not had a cluster period for many years.[56] Christiansen et al.[57] explored the possibility that long-term exposure to a long-acting nitrate (ISMN) could be a treatment of the cluster headache. Patients received 30 mg ISMN 3 times daily for 4 weeks in a double-blind, placebo-controlled, crossover design. There were a number of dropouts because patients could not tolerate the constant throbbing headache induced by ISMN. Strangely enough, patients experienced no initial increase in their cluster headache attack rate due to ISMN. In contrast, the daily nitrate-elicited headache diminished with time. GTN has been used to trigger cluster headache attacks in neuroimaging studies. Thus, it has been shown that a specific area in the hypothalamus is activated during GTN-induced cluster headache attacks.[58]

THE NO-cGMP CASCADE AS A TARGET FOR NEW DRUGS TREATING HEADACHES

The general possibilities for therapeutic strategies throughout the whole cascade of events initiated by NO have been summarized by Moncada and Higgs.[59] The following therapeutic strategies will be discussed: NO scavenging, NOS inhibition, inhibition of cofactors, degradation of cGMP, protein kinase inhibition, and antagonism of ion channels.

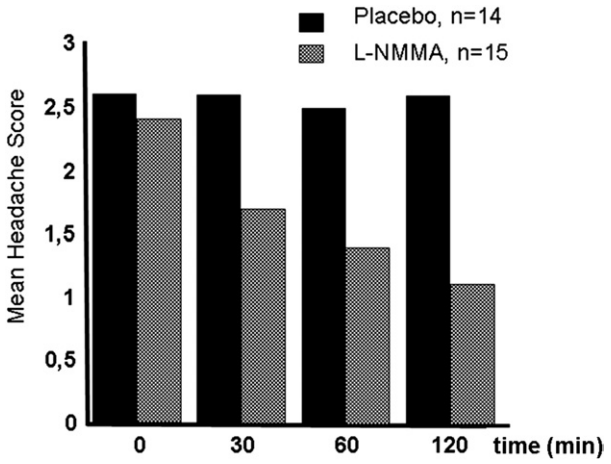

FIG. 3. The effect of L-nitromonomethylarginine (L-NMMA) was a nonselective inhibitor of all three nitric oxide synthase (NOS) enzymes. In this double-blind, clinical trial, spontaneous attacks of migraine without aura were treated with L-NMMA or a placebo in a group comparison experiment. On the x-axis, the headache was scored on a 0 to 3 verbal rating scale (no headache, mild, moderate, and severe as 0, 1, 2, and 3, respectively). The headache was progressively reduced by active treatment, but only a very modest change took place after the placebo. Thus, inhibition of all three NOS enzymes was effective in the treatment of migraine attacks. (From Lassen et al.,[60] with permission.)

Migraine

There are several reasons to believe that NO scavenging or NOS inhibition may be therapeutic in migraine. One reason is the great importance of NO in the mechanisms of migraine discussed in previous sections of this review. Even more important is the positive effect of nonselective NOS inhibition in migraine attacks shown by Lassen et al.[2,60] They treated patients with the nonselective NOS inhibitor L-NMMA in a dose considered maximal because it increased blood pressure significantly.[16] Two hours after treatment, migraine attacks overall had improved by 60% (FIG. 3). Although this evidence is fairly convincing, it must be pointed out that the trial was not a regular double-blind, controlled trial. It used only two placebo patients to blind the study and added historic control patients from earlier trials with an identical design. Thus, it can not be completely disregarded that a bias or different patient selection could have played a role. L-NMMA is not suitable as a drug because it is poorly absorbed by the oral route, it has a relatively short duration of action, and it increases blood pressure because it inhibits eNOS. Therefore, it was suggested that selective NOS inhibitors would be needed to develop useful antimigraine drugs.[60] It is still unknown whether inhibition of eNOS, nNOS, and/or iNOS provide the therapeutic effect in migraine. In this respect, Glaxo Smith Kline developed an iNOS inhibitor to be tested in migraine, but no results are in the public domain. Likewise, the biotech company Neuraxon developed highly selective nNOS inhibitors, but these have not been tested in migraine yet. Finally, eNOS inhibitors have not been tested yet, but they seem unsuitable because they increase systemic blood pressure.

NO scavenging might be another possible principle. In an open pilot study hydroxycobalamin (ie, an NO scavenger) reduced migraine attacks by more than 50% in half the patients[61]; nevertheless, this study is unconvincing because of its open nature. Moreover, superoxide scavenges NO and sumatriptan may scavenge superoxide, hydroxyl, and nitric oxide radicals in a dose-dependent manner.[62] Because sumatriptan can decrease cortical NO level,[63] its antimigraine action may involve a decrease in NO release and an increase in superoxide formation in cortex after cortical spreading depression.[64]

Tetrahyrobiopterin is the most important cofactor in the conversion of L-arginine to NO and L-citrulline. The chemistry of this compound has been thoroughly discussed elsewhere.[65] In most systems, this cofactor is rate limiting in the formation of NO and inhibition or removal of tetrahydrobiopterin; therefore, results in decreased production of NO might be therapeutic in migraine. Moreover, because NO activates soluble guanylyl cyclase leading to the formation of cGMP, inhibitors of cGMP might have therapeutic efficacy in the treatment of migraine. Another way of reducing cGMP is by increasing its breakdown by activation of phosphodiesterases. Further downstream, cGMP phosphorylates phosphokinase G, and hence inhibition of this phosphorylation, or of phosphokinase G in other ways, may potentially be of interest, but this has not been studied. The end result of the intracellular chain of events is a decrease of intracellular calcium. This probably happens via the opening of potassium channels. It has already been mentioned that at least part of the dilatory effect of NO is mediated via calcium-activated potassium channels because an antagonist of this channel partially blocks the effect of GTN in the closed cranial window migraine model.[21]

In conclusion, there are several potential targets in the NO-cGMP cascade for new antimigraine drugs, but it is not yet possible to judge the merits or side effects of each of these targets.

Tension-type headache

In the tension-type headache, evidence for involvement of NO is not quite as strong as it is in migraine, but as previously discussed there is one randomized, double-blind, crossover study indicating that GTN can induce tension-type headache.[52] Another randomized, double-blind, crossover, placebo-controlled trial showed that a single dose of the nonselective NOS inhibitor L-NMMA had a significant effect in chronic tension-type headache

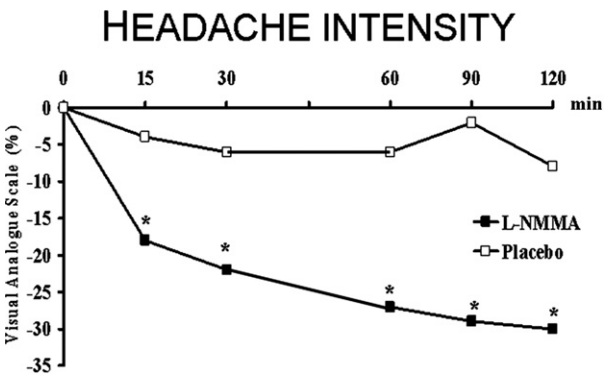

FIG. 4. In this double-blind, crossover experiment, patients with chronic, tension-type headache were treated with a placebo and L-monomethylarginine (L-NMMA). The x-axis represents the percent reduction in headache rated on a visual analogue scale. Pain was significantly reduced by L-NMMA compared to the placebo. Nonselective nitric oxide synthase (NOS) inhibition had an effect of 30% in this acute experiment, but this may have a much greater effect in a long-term study, which is yet to be done. (From Ashina et al.,[66] with permission.)

compared to the placebo (FIG. 4).[66] Both the area under the curve of headache intensity and peak headache were reduced, but the effect amounted to only 33%.

It remains to be seen whether a longer lasting treatment for the duration of several days might have a greater effect on this chronic condition. Whether inhibition of eNOS, nNOS, or iNOS, or a combination of these, might be responsible for the therapeutic effect also remains unknown. The possible use of NOS inhibitors for the treatment of chronic tension-type headache has been comprehensively discussed in a recent review.[67]

Cluster headache

As previously discussed, NO is also crucially involved in the mechanisms of cluster headache. There are no studies showing efficacy of NOS inhibition in spontaneous attacks of cluster headache. However, in one study the possibility that the development of tolerance to nitrates could be therapeutic was evaluated.[57] ISMN (30 mg) was administered orally 3 times daily for 4 weeks to nine sufferers of chronic cluster headache in a double-blind, randomized, placebo-controlled, crossover designed study. Blood velocity in the middle cerebral artery and the diameter of the temporal and radial arteries were repeatedly measured. Tolerance in the middle cerebral artery was complete within 24 h and in the temporal artery after 7 days, whereas tolerance of the radial artery was not observed. A close temporal association between the disappearance of nitrate-induced headache and tolerance of the temporal artery was observed, but tolerance had no effect on cluster headache attack frequency. Thus, tolerance to nitrates is not a therapeutic modality in cluster headache, but all the previously discussed possibilities for pharmacological intervention in migraine might also prove useful in cluster headache.

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