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A REVIEW ON REPORTED NITRIC OXIDE SYNTHASE INHIBITORS FOR TREATMENT OF MIGRAINE

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Abstract: **Migraine is one kind of chronic neurological disorder in which one experience reversible type of headache with neurological and systemic symptoms. The main symptoms includes fear of noise (phonophobia), sensitivity to light (photophobia), cutaneous allodynia, and some symptoms related to gastrointestinal tract (GIT) which includes emesis and nausea. The pain of migraine is not immediately experienced rather precursory symptoms can be experienced hours and days before the inception of pain. As per aspects of its pathophysiology the migraine attack can be split up into phases: the premonitory phases, the aura phase, headache phase and postdrome phase, respectively. The present studies involves study of pathology behind migraine attack along with role of nitric oxide synthase enzyme and also covers the detailed description of few reported molecules for inhibiting the action of nitric oxide synthase. We believe that this will help the in successfully design of new analogues.**

Keywords: **Amino acids; Headache; Nitric oxide synthase; Migraine; Peptides.**

1. INTRODUCTION

Migraine is identified as a chronic neurological disorder in which one experience either tolerable or severe headache with neurological and systemic symptoms which are generally reversible [1]. Some of the most common symptoms associated with migraine include fear of noise (phonophobia), sensitivity to light (photophobia), cutaneous allodynia, and some symptoms related to gastrointestinal tract (GIT) which includes emesis and nausea [2]. The pain of migraine is not immediately experienced rather precursory symptoms can be experienced hours and days before the inception of pain [3]. The most usual indications of migraine are difficultly in concentrating, stiffening of neck, always feeling tired (fatigue). The symptoms that can be experienced before the beginning of the pain can be categorized as psychological (depression, anxiety), cranial parasympathetic (lacrimation), neurological (photophobia), arousal (drowsiness), common symptoms (nausea, diarrhea, food craving and yawning etc) [4].

Patients suffering from migraine often distinguish it as unilateral that is pain is experienced only on one side in 60% cases, throbbing that is pulsating pain in 50% cases and pain that is increased by performing certain physical activities in 90% or movement of head [5]. Sometimes while experiencing the attacks headaches can vary from side to side. It is commonly observed that the potency of pain is either moderate or severe in most of the cases. The time within which the pain is experienced at its peak is 1 h and thereafter it is experienced for 24 hours [6]. The time duration for migraine varies in different age groups i.e 4 to 72 h in adults and 2to 48h in children. The most common regions of brain that experiences pain are the posterior cervical and trapezium regions [7]. It has been seen that about 75% of patients suffering from migraine have neck pain in common (Calhoun et al., 2010). Some symptoms like sinus or pressure experienced by around 40% patients [8] [9] and cranial autonomic features experienced by around 50% patients comes under commonly observed symptoms [10]. It is known to the one of the leading source for disability all around the world, as recognized by

the continuing studies conducted for risk factors, injuries, and global burden of diseases [11], especially for the segment of population younger than 50 years (Steiner et al., 2016). In survey conducted by WHO showed that the combination of severe migraine with psychosis, quadriplegia and dementia are proved to be the largest disabling chronic disorders [12]. It is observed that the prevalence of migraine is twice or thrice times more in women as compared to men [13]. Nitric oxide (NO) is commonly linked with headaches caused migraine [14] [15], as it has been involved in processing of pain [16]. According to the assembled evidenced it has been observed that NO has a major role in the pathophysiology of migraine by two methods either independently or by involving nitrergic cascade consisting of neurobiological processes and targeting elements that possibly lead to the production of potential therapies for the treatment of migraine headache. Over the last 20 years the main focus is towards the targeting of NO through various nitric oxide synthase inhibitors (NOS) for the treatment of migraine [17].

2. TYPES OF MIGRAINE

Migraine without aura (MO)

Migraine without aura previously known as common migraine is diagnosed by the fact that the patient is suffering from episodes of disabling headaches which has an ability last from few hours to few days along with gastrointestinal symptoms or intensified special senses [18]. If the pain experienced during migraine is mild or generalized then it can easily fulfill the criteria of The International Headache Society and thus nor necessarily have to be severe or unilateral [19]. During MO it is quite unusual to divert ones' pain by performing some exercise or doing any kind hard work like in tension type headache (TTH). The two important factors that contribute towards the diagnosis of migraine are frequency and periodicity of migraine [20]. If the patient is experiencing migraine-like headache more than two times per week, then there are chances that is might not be alone MO, but MO complicated by medication overuse headache (MOH) or TTH. It is generally in case of patients with "*intractable migraine*" or "*status migraineurs*"[21] .

Migraine with aura (MA)

In Migraine with aura previously known as focal or classical migraine, the aura can be seen to develop at a steady rate, and it can take upto few minutes [22]. It can be observed that when one feature of aura is improving other is deteriorating side by side. Visual auras can be diagnosed easily without any trouble, but it is opposite in the case of auras involved with sensation, cognition, movement, consciousness, or vestibular function that are often misunderstood by thromboembolism, epilepsy (commonly occipital seizures). Patients having recent onset MA, generally have a prolonged history of MO, and are sometimes diagnosed mistakenly by normal headaches, sinus infection (sinusitis) or bilious attacks [23]. People often see things which are not there, resulting to the conclusion of positive visual symptoms, binocular and homonymous, but often people hold on to the fact that it is due to monocular visual aura which leads to the possibility of retinal origin [24]. Migraine headache can usually be seen after aura, but aura can take place anytime in relation to pain. Aura not every time is contralateral to pain. Migraine aura without headache can be normally seen in middle age people in which a spurt of MA episodes without headache usually set off the referral fearing transient ischemic attacks (TIA) [25].

3. PATHOPHYSIOLOGY

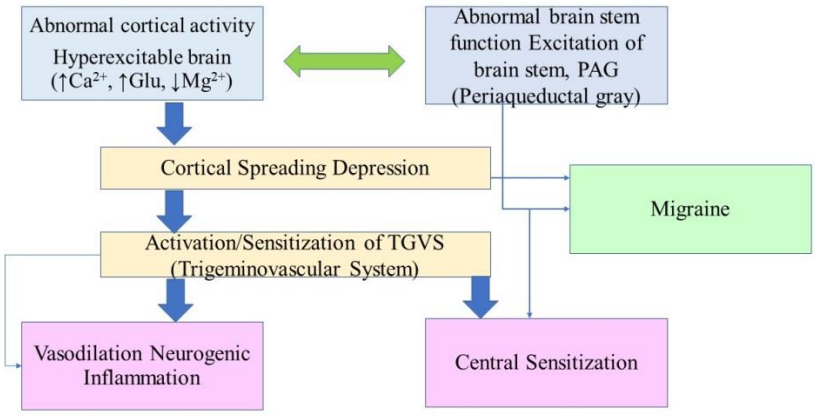


Figure 1: Pathogenesis of Migraine[26].

Migraine attack phases

Bases upon the limited relationship with headache, the migraine attack can be split up into phases: the premonitory phases (precede headache), the aura phase (immediately preceded or accompanies headache), headache phase (headache occurs) and postdrome phase (after the headache has been resolved) [27], it has been seen that before headache actually happens the headache phase changes continuously for hours in quantitative sensory thresholds, and constant with subjective sensory symptoms in premonitory phase [28] [29]. Different studies such as PET [30] and functional MRI [31] studies gives us an idea of changes, that occur in the activity and connectivity of hypothalamus in hours before headache occurs in case of triggered and spontaneous migraine attacks [32]. Polyuria and some changes like change in mood and appetite preceding headache can be the result of change in hypothalamic functions. Some correlations observed in PET studies of premonitory phases: increased activity in occipital cortex with that of sensitivity to light [33] and brainstem activation with nausea [34].

Thalamic and thalamo-cortical circuits

Electrophysiological studies show changes in the circuits that are responsible in establishing connection between thalamus and cortex all this happens during premonitory phase [35]. During and between the migraine attacks the structural and functional imaging studies conducted represents the differences in thalamic and thalamo-cortical activity in patients with migraine versus control group [36] [37] [38]. The studies also show that thalamus plays an integral role as mediator of cutaneous allodynia [39] and intensifying headache due to light [40]. Thus, these studies collectively lead to the result that both thalamic and thalamo-cortical activities are main causes for the abnormal sensory processing which is in short key feature of migraine attack [41].

Network connectivity

Resting state MRI has been used in the conduction of numerous studies to observe changes in the connectivity between different regions of brain before and during migraine attacks. Altered connectivity be observed through studies in parts like amygdale [42] [43] hypothalamus [44], brainstem [45], cortex [46] and cerebellum [47],constant with the changes in the function of multiple overlapping sensory and pain-processing circuits associated with mood and anxiety. While the consequences regarding changes associated with connectivity remains undetermined, chances are there that they might get involved in regulation of pain and sensory sensitivity which happens irately and interictally in patients of migraine. Another very common symptom associated with disability is cognitive impairments, and can also be held responsible for the disruption of normal brain function connectivity [48] [49].

Neck pain

From beginning of premonitory phase and throughout the postdrome phase, neck pain is the most commonly seen symptom for migraine and a major benefactor of disabilities related to migraine [50]. The pain inputs from trigeminal nerve on second order neurons in brainstem and upper cervical spinal cord merges with the pain from cervical nerves [51]. It has been observed that stimulation of cervical nerve triggers head pain in people with or without migraine, whereas patients suffering from migraine experience pain in the peri-orbital distribution upon C1 stimulation [52]. The possibility of criterion pattern is due to the central sensitization of the point where cervical and trigeminal inputs merge i.e., trigemino-cervical complex in addition to this another prominent contributing factor is the difference in the anatomy of upper cervical nerve roots, mainly C1 root in human beings [53]. Now this difference or the variability leads to a luring possibility that the pattern of migraine pain (involving headache) and specially its reaction to the local therapies (suboccipital injections) could be impacted by the structural differences in the cervical nerve roots. The branches of trigeminal nerve through skull are capable of reaching the neck musculature leading to a possibility that trigeminal afferents have role in pain related to migraine, according to the studies conducted for nerve tracing [54].

Mediators of migraine- Neuropeptides

Series of evidence shows the importance of calcitonin gene-related peptide (CGRP) as arbitrator of causing migraine and chief therapeutic target. According to the studies conducted it has been observed that during migraine or cluster headache attack when CGRP is released into the circulation, its concentration gets normalized with that triptan therapy unlike with a non-specific opioid analgesic [55]. Patients suffering from chronic migraine experience constant high levels of CGRP concentrations [56]. Some small-molecule CGRP antagonized have proved to but effective in the treatment of acute migraine therapies [57] [58] and inoculation of CGRP leads to delayed migraine in susceptible patients [59]. A peptide

release study conducted for 22 patients suffering from migraine manifested that the following concentrations were not elevated during migraine attacks- substance P, substance Y and vasoactive intestinal peptide. In this observation, it has been seen that release of CGRP is not a component of generalized neurogenic inflammation which was earlier defined on the basis of animal model primarily mediated as substance P [60] [61]. Numerous neurogenic inflammation inhibitors that are substance P receptor antagonists, in animal models showed no results in clinical trials of migraine therapies [62]. It is very important to study the efficacy of antibodies targeting CGRP or its receptors for a better view of pathophysiology of migraine. It is very unlike for CGRP in a very considerable amount to cross the blood-brain barrier (BBB), thus CGRP aiming outside of brain might help in prevention of migraine. However, the CGRP and its receptors on brain region like outside the BBB, which can be pineal gland, area postrema and median eminence can be targeted by antibodies [63]. There is evidence that trigeminal neurons can be inhibited by antibodies against CGRP like fremanezumab a CGRP antagonist inhibits the central trigeminovascular neurons activation with input from the intracranial dura, but not from cornea or facial skin [64]. It has been observed that pituitary adenylate cyclase-activating polypeptide (PACAP) when administered systematically like CGRP triggers migraine in susceptible individuals and high levels of PACAP are observed in patients of migraine during attack. Unlike in CGRP, some common responses like sustained vasodilation and generalized flushing can be seen on the administration of PACAP [65]

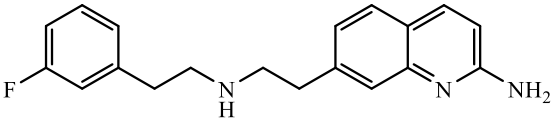
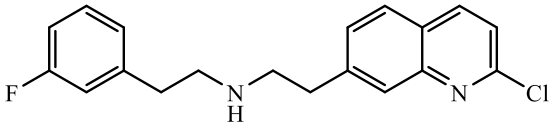
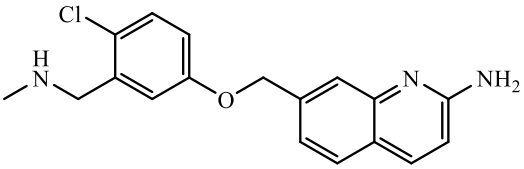
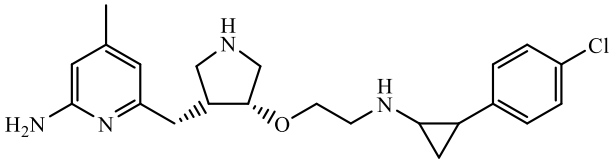
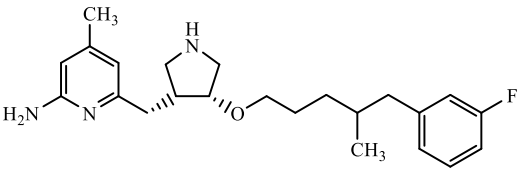
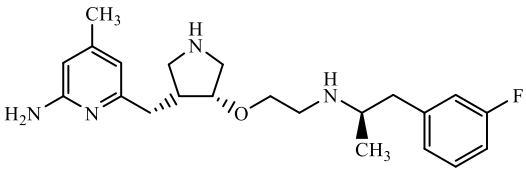
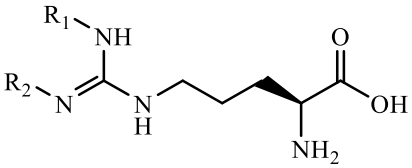
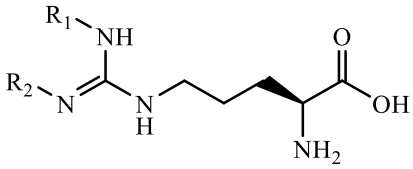
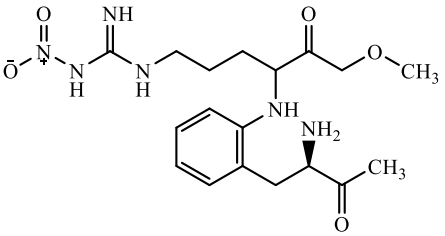
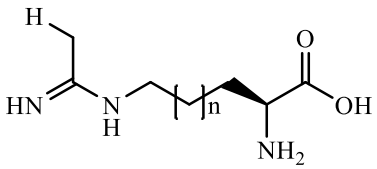
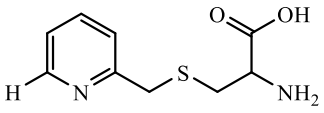
Nitric oxide synthase inhibitors

In year 2014 it was reported that 2-aminoquinoline analogues (compound 1 and 2) act as a competitive inhibitor for nitric oxide synthase **(**NOSs). Despite their promising potency those also have some associated effects like they work as strong binders with more than 100 nm affinity towards opioids, dopamine, histamine receptors, and norepinephrine (NE) transporters producing non favorable side effects. The development of these aminoquinoline analogues was carried out by taking clue from the earlier reported potent compound 3-5, whereas the binding activity along with isoform selectivity was improved via placing exterior polar group near to an interior hydrophobic group [66].

Further Cinelli and his group members evaluated the various 2-Aminoquinoline containing Aniline and phenyl ether analogues against neuronal nitric oxide synthase (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS) enzymes for the successful treatment of neurodegenerative disorders. Their results concluded that compound No (As per table 20) was most potent via substituting halogens *para* to phenyl ether linkage and has shown significant an extra van der Waals interaction with Tyr706 or surrounding hydrophobic structures with human nNOS inhibition at IC50 value of 0.295 µM 9 [67]. Li and their group members also developed a series of trans-cyclopropyl- and methyl-containing analogues using cis-3,4-pyrrolidine nucleus. Their study results showed that derivatives having adjacent amino group exhibits less activity those designed to lower the pKa. Nitric oxide hemoglobin capture assays results shows that three compounds (compound no 2d, 2e and 2f) showed significant better activity at IC_{50} values up to 0.70 µM. Among all most active compound was 2e that also exhibited amine-Glu592 interactions and presence of methyl groups also increases its binding affinity [68]. Simple arginine-based derivatives were primarily considered as inhibitors for the purpose of experimental use because they were considered to compete with arginine for active site of NOS. Some members of this group of inhibitor are capable of acting as the reaction based inhibitor [69]. The analogue L-N^{w}- Methylarginine (L-NMA compound 7) which is also known as N^{G}-monomethyl-L-arginine (L-NMMA) and is basically the outcome of arginine-methylated proteins' [70] degradation [71]. When the eighties were about to end, it is one of the first compound then used which was instinctively incorporated for the inhibition of NOSes. It can be used for the purpose of reaction-based inhibition of iNOS and nNOS but not for eNOS (Reif et al., 1995). L-N^{w}, N^{w}-Dimethylarginine (ADMA compound 8) is considered to be a nonspecific competitive inhibitor of NOSes. Although it has been seen that the synthesis of NO with ADMA has been studied effectively in cells. D-phenylalynyl-N^{w}-nitro-D-arginine methyl ester strongly inhibits the nNOS and eNOS but not iNOS. Amidino amino acids are synthetic compounds used for the inhibition of NOS except for one compound that is N^{5}-(1-iminoethyl)-L-ornithine (L-NIO also known as N^{G}-iminoethylornithine compound 9). Apart from this various amino acid sulphides, sulphoxide and sulphones are the non-physiological amino acids that are introduced as NOS inhibitors [72].

Aromatic amino acids compete with arginine for the active site of NOS. Two very potent compounds are developed from it but however they lack in the sensitivity among individual NOS isomers. Heterocyclic Amino Acids are basically synthetic based inhibitors which are formed by the combination of ornithine scaffold (compound 10), which can adjust or fitting in the arginine binding pocket with imidazole further capable of binding with heme iron[73].

Table 1: Representation of structures of nitric oxide synthase inhibitors

 Compound 1	 Compound 2
 Compound 20s	Compound 2d 
 **2e**	 **2f**
R_1: CH_3, R_2: H L-N^w- Methylarginine (L-NMA) 	R_1:CH, R_2: CH_3 L-N^w, N^w-Dimethylarginine (ADMA) 
D-phenylalynyl-N^w-nitro-D-argininemethylester 	N^5-(1-iminoethyl)-L-ornithine (L-NIO) 
(R)-2amino-3-[(pyridine-2-ylmethyl)thioprpanoic acid 	

4. CONCLUSION

Migraine attack can lead severe issues involving neurological symptoms. Migraine can be treated at a very early stage that is the premonitory phase of migraine attack which could be beneficial in finding new therapeutic targets. It is also assumed that enhanced understanding regarding migraine pathogenesis can help in development of potential therapies targeting nitric oxide synthase. There has been ample evidences to show that NO is the key mediator in beginning and maintenance of migraine. This review helps the readers to successfully plan effective strategy for designing new molecules against migraine based on inhibition of isoform.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

AUTHORS CONTRIBUTION

All the authors are involved completely in collection, procession of data and preparation of manuscript.

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