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A Review on Role of 5HT in Migraine

K. Yitzhak[1]*, B. Venkata Ramana[2], Venugopalaiah P[1], E. Vamsi Krishna[2]

[1]*Ratnam Institute of Pharmacy, Pidathapolur, Muthukur (M), Nellore, Andhra Pradesh, India-524346*
[2]*Sasthra college of Pharmaceutica l and Educational Research, Nellore, Andhra Pradesh, India-524346*

A B S T R A C T

Migraine is a syndrome that affects a significant fraction of the world population, with a higher prevalence in women (15%) than in men (6%). Approximately 70% of patients have a first-degree relative with a history of migraine. Migraine occurs with increased frequency in patients with mitochondrial disorders, such as Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis and Stroke like Episodes. Based on the clinical features of migraine, three distinct phases can be discerned: an initiating trigger, an aura and, finally, the headache. . Migraine headache is believed to be the result of abnormal activity in the brain that leads to dilation of the blood vessels on the surface of the brain as well as the tissues that surround the brain. 5-HT synthesis occurs in the entero chromaffin cells; it is then taken up, stored in and released by platelets. In the CNS, 5-HT is synthesized in neurons and is released as a NT. A local vasodilatation of the intracranial extracerebral blood vessels / meningeal blood vessel promoted by specific triggers, potassium channel gene $KCNN_3$ my thus be of pathophysiological importance in migraine (with and without aura) and in the near future migraine treatments.

Keywords: $KCNN_3$, CNS, 5-HT, Encephalopathy, Lactic Acidosis

A R T I C L E I N F O

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***Corresponding Author**
K. Yitzhak
Ratnam Institute of Pharmacy,
Pidathapolur, Muthukur (M), Nellore,
Andhra Pradesh, India-524346
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1. Introduction

Migraine is a syndrome that affects a significant fraction of the world population, with a higher prevalence in women (15%) than in men (6%) [1]. Migraine is characterised by an intense and throbbing unilateral headache associated with anorexia, nausea, vomiting, photophobia, phonophobia and/or diarrhoea (common migraine). Sometimes the headache may be preceded by a focal neurological phenomenon ("aura") followed by headache (classical migraine); this aura consists of certain motor (weakness or paralysis) and/or focal neurological (scintillanting scotoma) symptoms. Approximately 70% of patients have a first-degree relative with a history of migraine. The risk of migraine is increased 4-fold in relatives of people who have migraine with aura. [24] Although no genetic basis has been identified for common migraine, it generally demonstrates a maternal inheritance pattern.

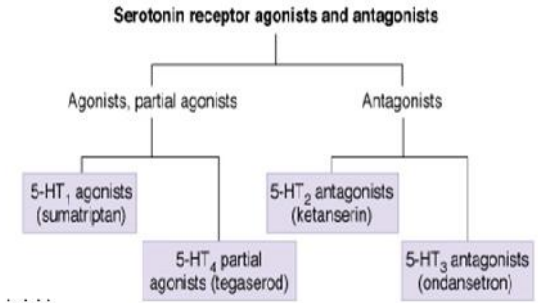

Figure 1: Serotonin Receptors

Serotonin (5-Hydroxytryptamine)
- An important neurotransmitter,
- A local hormone in the gut,
- A component of the platelet clotting process,
- Play a role in migraine headache.
- Mediators of the signs and symptoms of *carcinoi syndrome*.
- An unusual manifestation of carcinoid tumor,
- A neoplasm of enterochromaffin cells.

2. Etiology

Familial Hemiplegic Migraine:

Familial hemiplegic migraine (FHM) is a type of migraine with aura that is preceded or followed by hemiplegia, which typically resolves. Three loci have been identified in FHM. FHM type 1, which occurs in approximately 50% of affected families.FHM type 2 is due to mutation in the sodium channel gene *ATP1A2* on chromosome .[25] FHM3 is a rare subtype of FHM and is caused by mutations in a sodium channel α-subunit coding gene. Migraine occurs with increased frequency in patients with mitochondrial disorders, such as Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, And Stroke Like Episodes, Migraine is also a common symptom in other genetic vasculopathies.

Various precipitants of migraine events have been identified, as follows:

Table 1: precipitants of Migraine

Stress Excessive or insufficient sleep	**Medications (eg, vasodilators, oral contraceptives[28])**
Smoking	Exposure to bright or fluorescent lighting
Strong odors (eg, perfumes, colognes, petroleum distillates)	Hormonal changes, such as menstruation (common),[29] pregnancy, and ovulation
Head trauma	Weather changes
Metabolic or infectious diseases	Cold stimulus (eg, ice cream headaches)
Pickled fish	Fresh-baked breads

Migraine and other vascular disease:

People who suffer from migraine headaches are more likely to also have cardiovascular or cerebrovascular disease (ie, stroke and heart attacks). The physiopathology of the mechanism is still unknown. Reliable evidence comes from the Women's Health Study, which found that migraine with aura raised the risk of myocardial infarction by 91% and ischemic stroke by 108% and that migraine without aura raised both risks by approximately 25%. Migraines during pregnancy are also linked to stroke and vascular diseases. Migraine with aura for women in midlife has a statistical significant association with late-life vascular disease (infarcts) in the cerebellum. This association is not seen in migraine without aura.

Other Related Factors: In a population-based magnetic resonance had increased local iron deposits in the putamen, globus pallidus, and red nucleus, compared with controls.[34] This increase in iron deposits may be explained as a physiological response induced by repeated activation of nuclei involved in central pain processing or by the damage of these structures secondary to formation of

free radicals in oxidative stress, possibly the cause of chronification of the disease.[35]

3. Migraine Pathophysiology

Based on the clinical features of migraine, three distinct phases can be discerned: an initiating trigger, an aura and, finally, the headache. Although limited information is available about the trigger phase, there is indeed now a better understanding of the pathophysiology of migraine [20,21]. Some results indicate that the initiating trigger, involving the brainstem as 'migraine generator' [22], may be linked to a 'familial' channelopathy [23,21]. The subsequent events leading to the symptoms observed during the aura and headache phases can be explained on the basis of a neurovascular hypothesis [24,25,21]. Thus, as illustrated in Fig. (2), once the "migraine generator" has been switched on, regional cerebral blood flow decreases, possibly following a wave of cortical spreading depression [26].

Phases of Migraine:

a. The prodrome, which occurs hours or days before the headache
b. The aura, which immediately precedes the headache
c. The pain phase, also known as headache phase
d. The postdrome, the effects experienced following the end of a migraine attack
e. Noticeably, migraine attack consists of four phases, namely prodrome phase, aura phase, headache phase, and postdrome phase.

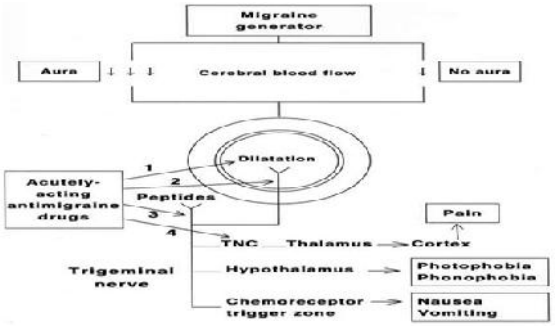

Figure 2: Diagram showing putative changes in migraine and the therapeutic targets of acutely acting antimigraine drugs. These drugs are believed to owe their antimigraine efficacy to direct vasoconstriction of dilated cranial blood vessels (1), inhibition of trigeminally-induced cranial vasodilatation (2), plasma protein extravasation (3) and/or central neuronal activity (4). Only lipophilic, brain penetrant triptans (not sumatriptan) exert central trigeminal inhibitory effects.

Cranial vasodilatation leads to enhanced blood volume following each cardiac stroke, with a consequent augmentation in pulsations within the affected blood vessels, as shown in Fig. (2). The augmented pulsations can then be sensed by "stretch" receptors in the vessel wall and the resultant increase in perivascular (trigeminal) sensory nerve activity provokes headache and other symptoms. This trigeminal stimulation may also release neuropeptides, thus reinforcing vasodilatation and perivascular nerve activity [for details and references, As illustrated in Fig. (2), within the framework of the neurovascular hypothesis of migraine, acutely acting antimigraine drugs (e.g. ergotamine) would constrict dilated cranial extra cerebral blood vessels reduce neuropeptide release and plasma protein extra vasation across dural vessels and inhibit impulse transmission centrally within the trigemino vascular system Noticeably, migraine attack consists of four phases, namely prodrome phase, aura phase, headache phase, and postdrome phase.

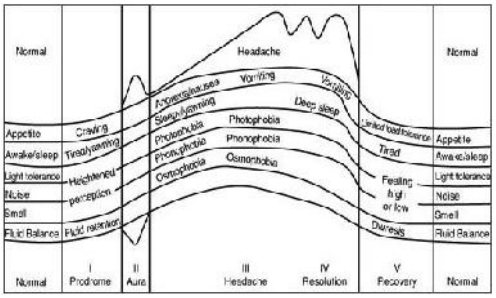

Figure 3: Symptoms and signs during phases of "Complete" migraine attacks with aura

Prodrome phase:

It is a forewarning phase that might occur 24 hours before the throbbing headache.[3,1] In this phase, changes in mood and appetite are observed, such us irritability, yawning, food cravings, depression, and other non specific symptoms.[1]

Aura phase

There are two main types of migraine; the classic (migraine with aura) and the common (migraine without aura). A third type of migraine is known as complicated migraine, which seams to share the same symptoms of classic migraine in addition to double vision and even loss of consciousness, but the pain will be located in the lower part of the brain or brainstem. This type is mostly diagnosed in teenaged girls.[7] In case of common migraine, a throbbing headache follows the prodrome phase within 24 hours without occurrence of aura. The aura phase in the classic migraine starts usually within an hour before pain onset; it might ends with headache or may occur while the patient is a sleep. Up to now, there are two kinds of known common aura; the visual and the non- visual aura. The visual aura is described as "heat" rising off pavement in the summertime, or as water cascading down a window pane or sparkling stars.

Headache phase

A typical migraine headache begins with mild pain grows to moderate or severe throbbing in character pain and intensifies by movement, which is combined with nausea and vomiting (sick headache). This severe pain is building up gradually and located in one side of the cranium and lasts between 4 to 72 hours. In some patients it starts with "switching sides" until it finally "picks a side", which is not the case in the other primary or secondary headache

disorders. However, "thunderclap" migraines can happen suddenly leading to onset of severe pain with or without aura. In this phase, the arteries dilate excessively after constriction in the aura phase. Migraineurs suffer from severe pulse headache as the pulse beat goes through a dilated sensitive artery. Those cranial sensitive arteries are pain sensitive structures in which the walls contain tiny nerve ending that go into the trigeminal nerve. After that, the pain becomes more diffuse and the inflammatory chemicals and cells (white cells) will accumulate into the nervous system covering the brain in an inflammation-muscle contraction stage. During the headache phase, the person might experience photophobia, hyperacusia, and muscle tenderness in the head and neck, in addition to autonomic disruption and clouding thoughts or mental functioning that might prolongs to persistent misery. All these symptoms are severe enough to introduce disability which forces the patient to confine to bed.

Postdrome phase

The also called "recovery phase" is characterized by exhaustion, dizziness, and irritability. This phase can take 48 hours or more. Migraineurs might have sick stomach, food intolerance, and decrease of concentration, occasional cognitive difficulties, and sore muscles. On the other hand, migraine patient might experience euphoria and sense of well- being during this phase.

4. Receptors and Effects

5-HT1 Receptors:

a. Most important in the brain.
b. Mediate synaptic inhibition via increased potassium conductance.
c. Mediate both excitatory and inhibitory effects in various smooth muscle tissues.
d. G-protein-coupled receptors.

5-HT2 Receptors

- Important in both brain and peripheral tissues.
- Mediate synaptic excitation in the CNS and smooth muscle contraction (gut, bronchi, uterus and vessels) or relaxation (other vessels).
- Mediates some of the vasodilation, diarrhea, and bronchoconstriction that occur as symptoms of carcinoid tumor.

5-HT3 Receptors

- Found in the CNS, especially in the chemoreceptive area and vomiting center, and in peripheral sensory and enteric nerves.
- These receptors mediate excitation via a 5-HT-gated cation channel.
- Antagonists acting at this receptor are useful antiemetic drugs.

5-HT4 Receptors

Found in the gastrointestinal tract and
Play a very important role in intestinal motility.

Role of Serotonin in the Different Organ Systems

a. There are a lot of receptors; at least 15 have been cloned at present.
b. Receptors are located widely throughout the CNS and periphery
c. Almost all receptors are G-coupled protein receptors
d. The one exception is the 5-HT3 receptor, which is an ionotropic receptor.
e. Current drug therapies are being designed that target specific receptor types.

Table 2: Role of Serotonin in the Different Organ Systems

What	Synthesis	CV	Hemostasis	GI	Physiology
Serotonin (5-HT)	Tryptophan-> 5-HT-> MOAA-> 5-HIAA Periphery: EC cells and Platelets CNS: NT	Vasoconstrictor and Vasospasm B-J Reflex	Promotes Platelet Aggregation	GI Motility Associated with Carcinoid Tumors Diarrhea and Nausea	Depression Chronic Pain Mania Anxiety,Appetite

Table 3: Trigger Factors

Migraine	**Trigger Factors**
Mental	Stress and Emotional upset
Endogenous	Hormonal Changes, Fasting, Fatigue, Sleep disturbances
Exogenous	Foods, Alcohol, Smoke, Allergens, Nitrates, O.C., Glutamate, Tyramine
Other	Weather, Bright Light, Odors, Temp Changes. Altitude

Evidence for a role for serotonin in migraine

During migraines there are changes in the blood levels of 5-HT and 5-HT metabolites; these changes are also seen in platelets and urine. Levels are increased before the headache and decreased during and after.

a. Migraines are associated with other behaviors and pathologies related to serotonin such as depression and sleep.
b. Drugs that cause 5-HT release can precipitate a migraine.

c. 5-HT receptors can be found on cerebral vessels and perivascular trigeminal pain nerves.
d. 5-HT has a known direct stimulatory effect on pain afferents, constricts cerebral vessels.
e. Drugs that are effective in migraine treatment have effects on one or more 5-HT receptors.
f. Differentiate the major clinical features of a migraine, including symptoms of classic and common migraines, and the migraine triggers.

Receptor	Location	Main effects	2nd messenger	Related to migraine
1A	CNS	Neural inhibition Behavioral effects: sleep, feeding, thermoregulation, anxiety.	?cAMP	no
1B	CNS Vascular smooth muscle	Presynaptic inhibition Behavioral effects Pulmonary vasoconstriction	?cAMP	yes
1D	CNS Blood vessels	Cerebral vasoconstriction Behavioral effects: locomotion	?cAMP	yes
1E	CNS, PNS	Not known	Not known	no
1F	CNS PNS (uterus, mesentery, artery) Vascular smooth muscle	Neurogenic inflammation	?cAMP	yes
2A	CNS PNS Smooth muscle Platelets	Neuronal excitation Behavioral effects Smooth muscle contraction (gut, bronchi, etc.) Vasoconstriction/ vasodilation	?IP_3/ DAG	no
2B	Gastric fundus	contraction	?IP_3/DAG	no
2C	CNS Choroid plexus	Cerebrospinal fluid secretion	?IP_3/DAG	no
3	PNS CNS	Neuronal excitation (autonomic, nociceptive neurons)	Non- ligand gated cation channel	no
4	PNS CNS	GI motility Neural excitation	?cAMP	no
5A	CNS Neuronal- like cells of the carotid body	Not known	?cAMP	no
5B	CNS	Not known	Not known	no
6	CNS	Not known	Not known	no
7	CNS PNS	Regulation of mood, learning, vegetative behaviors	?cAMP	yes

Figure 4: All 5-HT receptors, their locations, and effects are summarized

5. Conclusion

Migraine is a chronic condition of recurrent, throbbing headache generally felt on one side of the head but can also switch from one side to another. Migraines usually begin in early childhood adolescence or young adult life. The headache is characteristically accompanied by nausea, vomiting or loss of appetite. Activity, bright light or loud noises may make the headache worse, so migraineurs often seek out cool, dark, quiet rooms. Most migraine attacks are lasting from four to 12 hours, although shorter or much longer headaches can occur. It interferes with the physical ability to function, sometimes requiring bed rest. Although there are several kinds of migraines, the most common are classic migraine - a migraine with aura - and common migraine, which has no aura. Migraine attack consists of four phases, namely prodrome phase, aura phase, headache phase, and postdrome phase. Despite all the suggested hypotheses of migraine etiology, it remains unknown. Migraine headache is believed to be the result of abnormal activity in the brain that leads to dilation of the blood vessels on the surface of the brain as well as the tissues that surround the brain. The dilation of the blood vessels is believed to be associated with inflammation mechanism. This cerebral/ cranial vasodilation is referred to as “neurogenic inflammation”. Unfortunately, more is known about the factors involved in the pathophysiology of migraine headache pain after CNS dysfunction, and not before. In general, the mechanism of migraine attack is believed to consist of four steps after CNS dysfunction:

1) A local vasodilatation of the intracranial extracerebral blood vessels / meningeal blood vessel promoted by specific triggers.
2) Stimulation of pain pathways of the surrounding trigeminal sensory nervous through sensory nerve discharge causing pain impulses to be transmitted to caudal brain stem nuclei
3) Increased pain response by neuroinflammation process and release of the vasoactive neuropeptides (CGRP, NK_1, and SP).
4) Transportation of pain signals to higher centers where headache pain is recognized due to trigeminal nerves activation.

The new discovery of mutations in the calcium channel gene CACNA1A in migraineurs with familial hemiplegic migraine (FHM) gives link to suggest that migraine (with and without aura) is caused by ion channel abnormalities. This gene plays a critical role in determining the firing outline of neurons and acts to regulate intracellular calcium channels. This potassium channel gene KCNN3 my thus be of pathophysiological importance in migraine (with and without aura) and in the near future migraine treatments.

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