Physiological basis and Mechanism of Headache: Mini Review

Authors
Abhishek Sinha¹, Renu Bhatia²

¹Assistant Professor, Department of Physiology, Santosh Medical College, Ghaziabad, India
²Associate Professor, Department of Physiology, All India Institute of Medical Sciences, New Delhi, India

*Corresponding Author
Abhishek Sinha
Email: abhisheksinha@gmail.com

Abstract
Headache is one of the most common medical complaints of the general population. It could be a major symptom of a serious problem like subarachnoid haemorrhage or psychological factors like day to day tension. The knowledge of physiological basis and mechanism of various types of headaches like Migraine, Cluster headache and Tension type headache has been discussed in this article with recent insights and current understanding with new and old evidences. The present article is an attempt to broadly cover this aspect.

Keywords: Headache, Migraine, Tension type headache, Cluster headache, Physiological basis, Pathophysiological mechanism.

Introduction
Headache is one of the most common medical complaint of general population. It is an excellent example of a problem that spans the breadth of medicine. It could be one of the major symptoms off a serious problem like subarachnoid haemorrhage or could simply be due to psychological factors such as day to day tension, without any organic disorder. The general knowledge of pain and nociception has improved dramatically in the recent decades however the understanding of physiological basis and underlying mechanism of headache has become essential in order to discover new treatment modalities which are aimed at relieving headaches.

The pain sensing receptors or nociceptors are present in various structures. The most important structures which register pain are the blood vessels, primarily the proximal part of cerebral and dural arteries along with them large veins and venous sinuses also have nociceptors. Cranial bone is insensitive but pain is experienced when periosteum is stretched. Direct stimulation of cerebral cortex, ependymal lining of ventricles and choroids does not cause pain.

As far as peripheral innervation is concerned, pain from upper surface of tentorium of anterior and middle cranial fossa is transmitted by trigeminal nerve. From the extra cranial arteries like supraorbital, frontal and superficial temporal, pain is transmitted by trigeminal nerve whereas the pain sensations from posterior auricular and occipital arteries is mediated by upper cervical roots. Other extra cranial structures like upper cervical, spine,
eyes, nasal sinuses and teeth also convey pain sensations via cervical and trigeminal nerves\(^{(1)}\). The main afferent pathway from the anterior two thirds of the head is the ophthalmic division of trigeminal nerve. The central axon of the cell body in trigeminal ganglion descends in the spinal tract of the trigeminal nerve to the second cervical cord segment where fibre from occipital region traverse the dorsal root ganglion to converge on the second order neurons, from here the impulses go to the ventro-postero-medial nucleus of thalamus\(^{(1)}\). The transmission of this synapse is controlled by the endogenous pain control system descending from the PAG (Periaqueductal grey) and region of locus ceruleus\(^{(1)}\). Finally, the impulses go to the sensory cortex, frontal cortex, visual and auditory association areas, anterior cingulate cortex and basal ganglia\(^{(1)}\).

The most common headaches are Migraine, Cluster headache and Tension type headache which are also called as Primary headache disorders, different from secondary headaches (those which arise as a consequence of some intracranial/extra cranial pathology). The main factors which cause headaches are vascular, chemical, humoral, endogenous opioids system, autonomic nervous system, psychological and muscle contraction.

**Review**

**Migraine**

The term “migraine” is derived from the Greek word Hemicranial, introduced by Galen in approximately 200 AD. Migraine is a common episodic headache disorder characterised by attacks consisting of various combinations of headache and neurologic, gastrointestinal and autonomic symptoms. Most patients develop migraine in first three decades of life. Each episode of headache generally consists of unilateral throbbing pain of moderate intensity which is aggravated by movement and associated with either nausea or vomiting or photophobia and phonophobia\(^{(2)}\). Migraine is primarily considered a neuromuscular headache characterised by unilateral throbbing kind of head pain. The pathogenesis of migraine primarily involves

I. Chemical changes: The brain phosphates were measured by nuclear magnetic resonance imaging after intravenous injection of P\(^{31}\) has enabled the indirect assay of magnesium content by examining the chemical shift properties of the P\(^{31}\) resonance signals. The technique was used by Welch et al.,\(^{(3)}\) and they reported low concentration of magnesium responsible for cerebral excitability.

II. Neurophysiological changes: The contingent negative variation, a slow event related potential is enhanced in migraine patients. This event is thought to be mediated by noradrenergic pathway\(^{(4)}\). The amplitude difference between the primary positive and negative waves of the visual evoked response is increased in migraine subjects.

III. Central changes: These include hypothalamic-pituitary axis and dopaminergic transmission. The excitatory 5-Hydroxytryptamine (5-HT) mediated mechanisms are more predominant over inhibitory dopaminergic mechanisms. There are reports of suppressed prolactin secretion by dopaminergic agents in women with migraine. Present information suggests a dopamine deficiency in migraine with super sensitivity of dopaminergic receptors\(^{(5)}\). Endogenous opioids like beta-endorphin, enkephalin and dynorphins are inhibitory neurotransmitters implicated in central regulation. According to vascular theory of Wolff\(^{(1)}\), the vasoconstrictor phase of migraine prodrome is due to neuronal release of Norepinephrine which causes vasoconstriction via alpha-adrenergic receptors. By contrast, the painful phase of migraine was attributed to a painful vasodilation of extra cranial arteries. Recent clinical studies have revealed that the levels of Anandamide (AEA) are decreased in CSF and plasma of chronic migraine patients.\(^{(6)}\)

IV. Muscle contraction: An over activity of cervical muscles and presence of myofacial
trigger points has been reported as a cause of migraine pathology\(^{(7)}\).

V. Nitric oxide: Recently endogenous nitric oxide (NO) has been implicated in the pathogenesis of migraine. The endothelium nitric oxide synthase is stimulated by an increase in intracellular calcium ions. This increase may be caused by shear stress and receptor stimulation (Histamine, Bradykinin, Substance P and Acetylcholine). NO diffuses from endothelial cells to smooth muscle cells and activates the soluble guanylate cyclase hence other downstream events of vasodilation. Other factors include genetic factors specifically the MTHFR, KCNK18, TRPV1, TRPV3 genes\(^{(8)}\) and calcitonin gene-related peptide (CGRP) can be a likely candidate for therapeutic blockage as it has been shown to released during migraine attack\(^{(9)}\).

VI. Humoral factors: Recent studies indicate the role of hypertension and obesity in migraine due to altered insulin receptor singling and physiological response\(^{(10)}\).

By intravenous infusion of GTN, a reproducible experimental model of headache has been produced and it has been seen that patients suffering from migraine are more sensitive to GTN induced headache. It is well known that GTN induced vasodilation is via NO-GMP cascade. NO is produced in platelets during migraine attacks. It may also be related to the migrainous pain and the changes in cerebral blood flow experienced during migraine attacks\(^{(11)}\).

It increases the nociceptive sensitivity in the central nervous system and animal studies suggest that NO plays an important role in central modulation of nociception and produces hyperalgesia. It is concluded that the pathogenesis of migraine might not be only due to vascular factors but also chemical, neurophysiological, autonomic and peripheral factors.

Cluster headache

Another common type of headache disorder is cluster headache. It is characterised by localised pain on one side of head along with features of ocular, nasal, gastrointestinal, vascular and neurological systems. The basic mechanism besides vascular factors is the involvement of the autonomic nervous system\(^{(12)}\). The spinal tract and the nucleus of the trigeminal nerve descending to the C2 segment becomes hyperactive unilaterally during cluster headache and the main peripheral source of pain is internal carotid artery and its branches\(^{(13),(14)}\). The pathogenesis of Cluster headache primarily involves:

I. Vascular: Among the vascular factors the dilation of proximal branches of internal carotid artery and the capillary dilation of ipsilateral conjunctiva, nasal mucosa and cutaneous circulation in periorbital area is implicated in the pathogenesis of migraine. The autonomic nervous system involvement has also been implicated in pathogenesis of cluster headache. It has been studied that sympathetic block at the level of C7 can treat an attack of cluster headache\(^{(15)}\).

II. Central: The central factors are important since there is a daily rhythm existing for such headaches. The daily rhythm is operated by suprachiasmatic nucleus of the biological clock, hypothalamus. Certain studies have been shown lower levels of melatonin at night in cluster headache and melatonin may play a role in management of this headache\(^{(16)}\).

III. Autonomic nervous system: The headache is reported to coexist with Horner’s syndrome which is characterised by autonomic nervous system abnormalities\(^{(17)}\).

IV. Genetic factors: MTHFR, KCNK18, TRPV1, TRPV3 genes\(^{(8)}\) have been reported to have a role in these patients.

Tension type headache (TTH)

Tension type headache is characterised by a band like pain experienced in frontal, parietal and occipital regions, the duration of attacks ranging from
few hours to several weeks (15 days per month for 6 months or 180 days per year) which is not associated with any underlying disease \(^{(18)}\).

The International Society have designated the term Tension type headache to embrace a number of commonly used terms including tension headache, ordinary headache and psychogenic headache. It is generally recognised that there may be myogenic and psychogenic factors of variable importance \(^{(4)}\). This type of headache is a typically pressing or tightening in quality, may be mild to moderate in intensity and usually bilateral in location and does not worsen with physical activity \(^{(19)}\). The pathogenesis of tension type headache primarily involves:

I. Muscular: The mechanism of tension type headache remains to be determined. The previous term for this disorder “tension headache” was coined because the pericranial and cervical muscles were thought to be involved(muscle contraction headache). EMG studies support this hypothesis although certain studies indicate that EMG activity does not appear to be linked to symptoms of tension headache \(^{(20)}\).

It is still debatable whether the pain in tension type headache originate from myofascial tissue or it has a central component. The quality of pain also supports its aetiology in muscles. The pain is dull ach- ing and cramping in quality. It is difficult to localise the pain and also the pain gets referred to other sites like cervical region. On the other hand, there are typical features of muscle pathogenesis that clearly distinguish it from cutaneous pain, which is sharp, stabbing in nature is accurately localised to the site of lesion and is not referred to other sites. Therefore, it is quite clear that the pain in tension type headache is similar to myofascial pain elicited from other parts of the body. Whether it is strictly localised to muscle tissues or to other deep tissues is still unclear \(^{(19)}\). In addition, although the pain clinically resembles pain from myofascial tissues, as evident by the presence of myofascial trigger points (TRPs) \(^{(7)}\). TRPs through a peripheral mechanism have been shown to act on the trigeminal nucleus caudalis and which can lead to an attack \(^{(21)}\).

The role of EMG in assessing the muscle spasm in the chronic TTH patients still remains controversial. There are reports of over activity of pericranial muscles even at rest and feeling of fatigue during maximal voluntary contraction but the severity of headache is not correlated with EMG amplitudes \(^{(22)}\). We have also reported an over activity of pericranial muscles at rest in patients of CTTH \(^{(23)}\). One of the most consistent abnormality in chronic TTH is reduction or abolition of the second exteroceptive suppression period of temporals muscle (ES2) \(^{(24)}\). Exteroceptive suppression is the inhibition of voluntary EMG activity of the temporals muscle induced by trigeminal nerve stimulation. ES2 is a multi synaptic reflex, subject to limbic and other modulation was absent in 40% of TTH patients and reduced in duration in 87% of the patients. Schoenen et al \(^{(24)}\) reported that duration of ES2 was reduced in 87% of patients of chronic headache.

The exteroceptive suppression periods of temporals muscle activity are mediated in the brain stem by various oligosynaptic and multi synaptic pathways which receive a strong input from the limbic system, periacqueductal grey, amygdala and hypothal- amus. These regions are known to exert their influence in the modulation of nociception and PAG is involved in endogenous opioid mediated pain control mechanisms. The pathology is unsettled and increase in muscle activity is sometimes demonstrable in EMG \(^{(25)}, (26)\). 

Psychological

Since stress, mental tension and tiredness are the most important precipitating factors, therefore the possibility of central supra spinal factors involvement is implied. A specific analysis of relation between peripheral, spinal and supra spinal contributions to pain needs to be explored in more detail \(^{(27)}\). Chronic tension type headache is also associated with a feeling of fatigue and tension by many subjects. In a study conducted by Dallos et al \(^{(22)}\) fatigue correlated quite strongly with headache whereas
some patients reported associated tension with existing headache. Besides these subjective complaints of fatigue and mental tension it has been reported that there exists a role of endogenous pain control mechanisms in the pathogenesis of tension type headache. Endogenous opioids

The results of Naloxone challenge test reveal an abnormality in the endogenous opioid status of CTTH patients when compared with healthy control subjects. Whether or not the tension type headaches has a central origin still remains a question. The nociceptive flexor reflex, a spinally organised reflex was reported to be decreased in patients with chronic TTH\(^{(28)}\). As this reflex is influenced by endogenous pain control mechanisms, a defect either in opioid system or in the production of neurotransmitters was suspected. Furthermore, the findings of increased met-enkephalin levels in CSF from these patients support this idea\(^{(29)}\). Therefore, it is suggested that chronic tension type headache could be due to muscular factors or abnormal central pain control mechanisms\(^{(27)},(30)\).

**Conclusion**

Headache is a common neurological condition which can have multiple etiologies. Vascular, chemical, central, peripheral or psychological factors could lead to headache. A careful history and relevant investigations can help in understanding the pathophysiology and management of headache disorders.

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**Abbreviations**

MHTFR gene: methylenetetrahydrofolate reductase, KCNK18 gene: potassium channel, sub-family K member 18, TRPV1: transient related potential vanilloid type 1, TRPV3: transient related potential vanilloid type 3