CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2587036

Available online at: http://www.iajps.com Review Article

CHALLENGES IN BRAIN DELIVERY OF ANTI-MIGRAINE DRUGS AND CURRENT INITIATIVES TO IMPROVE THERAPEUTIC OUTCOMES

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Article Received: February 2019 **Accepted:** February 2019 **Published:**March 2019

Abstract:

Migraine is a common headache which is usually associated with nausea, photophobia and impaired daily activities. However, migraine can be extremely disabling with a considerable impact on the life of an individual in their ability to work. The arrival of triptans in the early 1990s saw a major change in the way migraines were treated, and triptans remain the gold standard in treating an acute attack. In recent times, considerable research has been made in understanding the pathophysiology of migraine. Numerous drug delivery systems have been discovered as therapies for brain disorders which may improve efficacy and reduce the toxic effect of the active compound. The blood brain barrier (BBB) is the most vital elements present in the central nervous system (CNS) which selectively permits the access of preferred molecules from blood to brain. The coming decade will see dramatic improvement in treating and preventing migraine with potential neuro-pharmacological agent and neuro stimulation. This article briefly discusses the different strategies for site specific delivery of anti migrane drugs in treatment of migraine in addition to the pathophysiology and management of migraine.

Keywords: *Migraine;Triptans; Bbb(Blood Brain Barrier);Neuro-Pharmacological Agent;Specific Delivery.*

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Please cite this article in press Harshitha V and V Kusum Devi., ***Challenges In Brain Delivery Of Anti-Migraine Drugs And Current Initiatives To Improve Therapeutic Outcomes.,*** *Indo Am. J. P. Sci, 2019; 06(03).*

INTRODUCTION:

Migraine headache is one of the most common, yet potentially debilitating disorders encountered in primary care (Benjamin Gilmore et al., 2011).

Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headache. It is the most common headache disorder, prevalent in 18% of females and 6% of males. These headaches are often in association with a number of autonomic nervous system symptoms (M. Srujan Kumar et al., 2015). The disorder is characterized by recurrent attacks lasting from 4–72 hours, of a pulsating quality, moderate or severe intensity aggravated by routine physical activity (Bhupendra Shah et al., 2017). Migraine is the commonest cause of recurrent, severe headache. The tendency to suffering from migraine has a genetic basis, but individual attacks may be triggered by internal or external influences, or simply happen with no apparent reason.

The pain of migraine is typically accompanied by other features such as nausea, dizziness, extreme sensitivity to lights, noises, and smells, lack of appetite, disturbances of bowel function, and so on. The typical constellation of symptoms experienced by migraine sufferers is reflected in the ICHD(International Classification of Headache Disorders diagnostic criteria for migraine).

Only about 20% of migraine sufferers experience aura, usually (but not invariably) before the headache starts. Most aura is visual, consisting of a combination of positive visual phenomena (floaters, flashes of light, moving or expanding zig-zag patterns, and so on) and negative phenomena (loss of vision causing blind spots). Many sufferers also experience sensory aura, consisting of tingling and numbness, often spreading over the hand, arm, face, lips and tongue on one side of the body. Weakness, dysphasia, and other aura symptoms are rare.

Between 10% and 20% of migrainers experience premonitory symptoms up to 48 hr before their migraines. These may include fatigue or abnormal bursts of energy, neck stiffness, yawning and frequent urination. Particular areas of the brain have now been identified that are active during the premonitory phase (Mark W. Weatherall,2015)

Pathophysiology of migraine

Brain, within the cranium, has meninges which comprises of arachnoid, dura mater and pia mater. As the brain is pain insensitive, these tissues are reported to be liable for the throbbing headache pain that occurs during migraine attack. The meninges are compactly innervated by small trigeminal axons, which bifurcate to middle cerebral and meningeal arteries in the proximity. Brain stem nuclei in its normal state, controls the vascularity of brain and regulates antinociception. Human migraine was thoroughly investigated using positron emission tomography as a tool to observe the alteration in blood flowing through the cerebral region during a spontaneous migraine attack activation.

They found enhanced blood flow in some portions of brain, such as cerebral hemispheres in cingulated, auditory, visual association cortices and also in the brain stem nuclei. Upon injection of sumatriptan, symptoms of headache, phonophobia and photophobia were relieved but the brain stem activation persisted even after that. This made them conclude that the imbalance in the activity of brain stem played a central role in the pathogenesis of migraine. CSD (Cortical Spreading Depression) seems to be one of the basic mechanisms for the initiation of a migraine attack. CSD triggers the trigeminovascular system which in turn releases nitric oxide and calcitonin gene related peptide (CGRP) thus inducing vasodilation and perivascular nerve activity (Priti Girotra et al., 2014)

The central nervous system (CNS) is involved in the migraine aura and 82% of patients have premonitory symptoms. The complex relationship between the CNS and peripheral nociception, including activation of sensory fibres and dilation of cranial vessels, remains to be elucidated. Migraine pain has been suggested to involve intracranial vessels, trigeminal sensory innervation and the reflex connection of the trigeminal system, and the cranial parasympathetic autonomic nerves (L.Edvinsson et al., 2008)

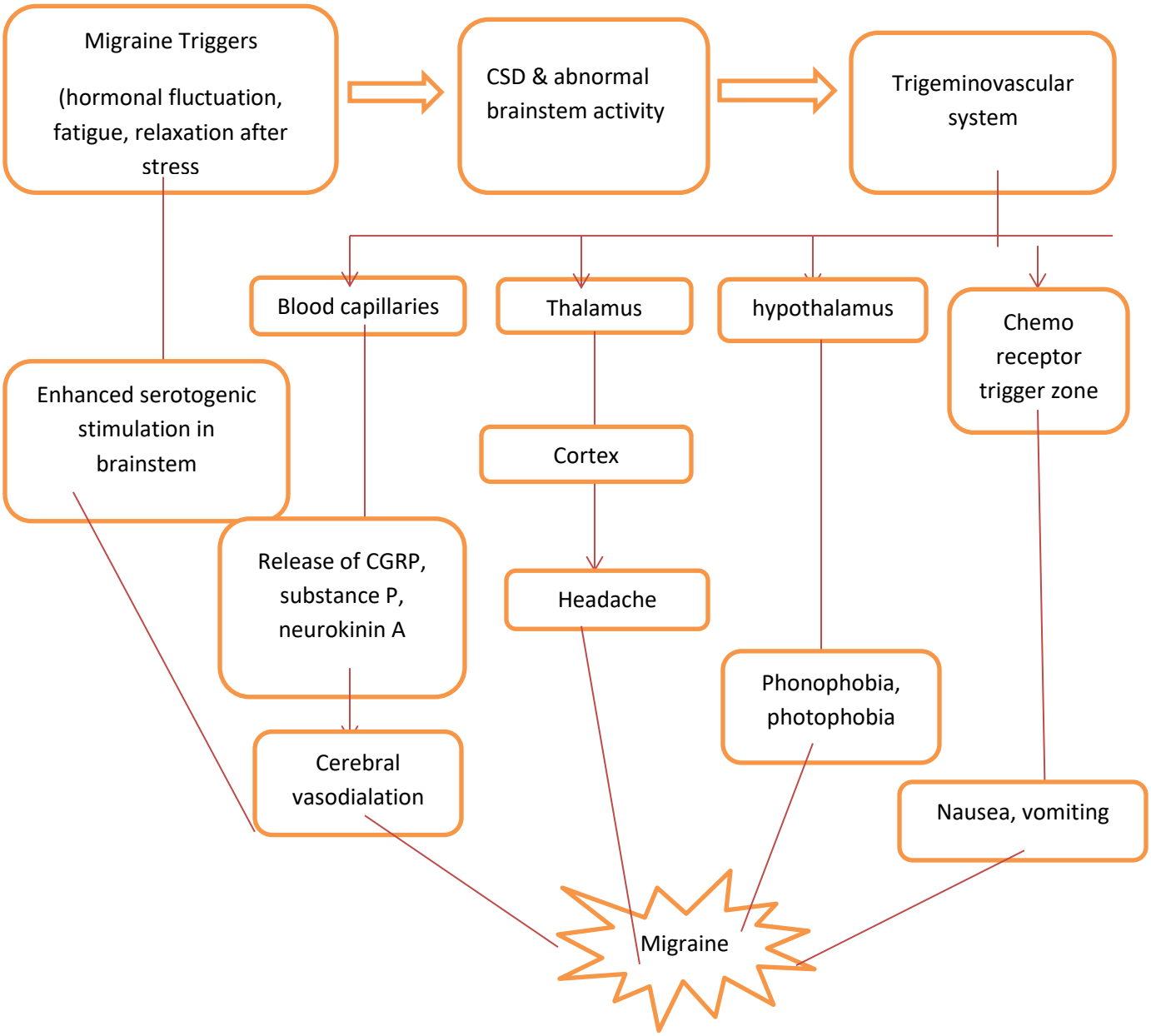

Figure 1. Schematic representation of pathophysiology of migraine

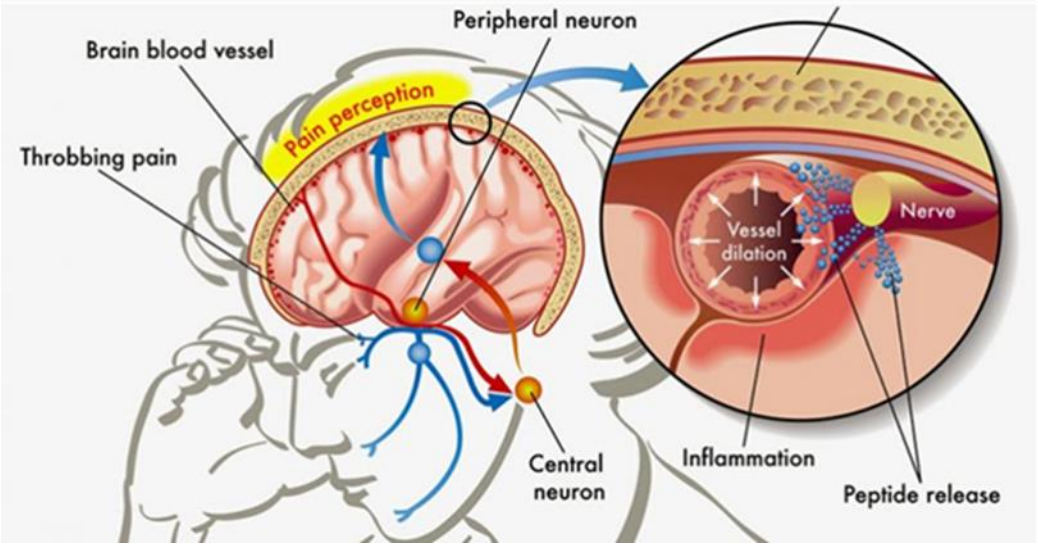

Figure 2. Vasodialated blood vessels

Management of migraine

Migraine can be managed pharmacologically or non-pharmacologically.

Non-pharmacological treatment

Non-pharmacological treatment of migraine includes a variety of psychological interventions with varying levels of evidence supporting their use. Relaxation, biofeedback, and cognitive behavioral therapy are recommended and effective. They can improve the patient's quality of life. Studies evaluating acupuncture are inconclusive, while homeopathy is proved to be ineffective (Khalid W. Al-Quliti et al., 2016)

Relaxation:

There are several methods that can be tried to relax or reduce stress, including breathing exercises, progressive muscle relaxation. Alternative therapies, including physical therapy, massage, hypnosis, chiropractic manipulation, acupuncture/acupressure, aromatherapy, and herbal therapy.

Biofeedback:

Biofeedback is typically used to treat chronic pain and people dealing with high levels of stress. With the assistance of a biofeedback therapist, patients are connected to electrical sensors that receive information (feedback) about the body (bio). This feedback helps to focus on making subtle changes in the body, such as relaxing certain muscles to release stress and lessen pain symptoms. The goal of this alternative therapy is to teach people how to control bodily responses easing tight muscles and to prevent and lessen headache.

Cognitive behavioral therapy:

Cognitive therapy mainly involves patients recognition of any negative thoughts associated with the stressors and teaches patients how to maintain a positive mood. It provides an insight into sources of stress and other triggers and the development of headache(www.clevelandclinic.com)

Pharmacological treatment

The pharmacological treatment encompasses prophylactic and abortive drugs. Additionally, the US Food and Drug Administration (FDA) have recently approved new therapies as well (Khalid W. Al-Quliti et al., 2016).

A. Prophylactic treatment

If the frequency, duration, and severity of the patient's migraine attacks are bad enough, consideration should be given to preventive therapy in which medications are given on a regular basis whether or not the patient has a headache.

Guidelines for the use of preventive therapy include: when a patient has more than four to six headache days per month; when symptomatic medications are contraindicated or ineffective; when acute medication is required more than twice a week; and for rare types of migraine including hemiplegic migraine, basilar migraine, migraine with prolonged aura, and migraine associated with cerebral infarction(J. D. Bartleson et al.,2010). Drugs that are given for prophylaxis of attack include propranolol, amitriptyline, flunarizine, and cyroheptadine. The mechanism of action is depicted in table 1.

Table1. Mechanism of action of prophylaxis drugs

Sl. no	Pharmacological class	Drugs	Mechanism of action
1.	Calcium channel blocker	Flunarizine	Reduction of cortical spreading depression and inhibition of neuronal excitability. It also raises the migraine threshold.
2.	β-blocker	Propranolol	Still not clearly established, but the most probable mechanism is the reduction of brain catecholamine activity.
3.	Seretonergic and noradrenergic reuptake inhibitor (SNRI)	Amitriptyline	It augments the potential of noxious inhibitory control neurons, blocks the peripheral sensitization, enhances the descending inhibition of rostroventromedial (RMV) nuclear complex, down regulates 5HT2 receptor and potentiates the GABA mediated inhibition.
4.	$5HT_2$ Receptor antagonist	Cyroheptadine	Mechanism not clear.

B. Acute (abortive) treatment

Abortive medications for migraine can be classified into; first line and second line drugs, or specific and nonspecific drugs. Nonspecific drugs are analgesics and anti-inflammatory drugs, while specific treatments include drugs like ergots or triptans, which target 5HT1 receptors specifically.

i)Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are recommended for treating acute migraine, these include: naproxen, ibuprofen, diclofenac. Their efficacy increases when combined with triptans. They are excellent in treating young individuals who can tolerate their gastrointestinal side effects, and ibuprofen can be used safely in children. Gastrointestinal side effects are more common with naproxen. Aspirin can be used as a single abortive agent or combined with metoclopramide (Khalid W. Al-Quliti et al.,2016). They act by Prostanoid receptor antagonists block prostacyclin (PGI2) receptors, which induces headache by vasodilation (Priti Girotra et al., 2014).

ii)Triptans

The mechanism of action of 5HT 1B/1D receptor agonists, or triptans , provide insights into the pathophysiology of migraine. The triptan have at least 3 distinct modes of action, all of which may be additive in their antimigraine effects.

The effects include vasoconstriction of painfully distended intracranial extracerebral vessels by a direct effect on vascular smooth muscle, inhibition of the release of vasoactive neuropeptides by trigeminal terminals innervating the intracranial vessels and dura mater, and inhibition of nociceptive neurotransmission within the trigeminocervical complex in the brainstem and upper spinal cord. Other possible antimigraine effects of triptans include modulation of nitric oxide-dependent signal transduction pathways, nitric oxide scavenging in the brain, and sodium dependent cell metabolic activity(Stewart J. Tepper et al.,2002).

Triptans offer benefits to patients with migraine that are similar in magnitude to the benefit levodopa provides to patients with Parkinson's disease. There are seven different triptans . All are 5-HT1B/1D receptor agonists. The potential mechanisms of action include cranial vasoconstriction and inhibition of peripheral and central trigeminal nerve transmission. All triptans are available in pill form. Only one can be administered by injection (sumatriptan), two are available as a nasal spray (sumatriptan and zolmitriptan), and two are available in an oral-dissolving tablet (rizatriptan and zolmitriptan).

Triptans reverse nausea and pain while leaving the patient clear-headed; they also are nonaddictive. Triptans provide substantial headache relief in up to three-fourths of patients. Many patients who have menstrually associated migraine attacks can be successfully treated with a triptan. In general, almotriptan, eletriptan, and rizatriptan are probably the most effective triptans(Priti Girotra et al., 2014).

iii) Ergot derivatives

Ergot derivatives are the oldest compounds used for treatment of migraine. Dihydroergotamine is well tolerated and can be given intramuscularly (IM), intravenously (IV), or nasally; ergotamine is available in tablet format. These compounds are contraindicated in patients with hypertension, coronary artery disease, or other cardiovascular risk conditions (Khalid W. Al-Quliti et al., 2016). Ergot derivatives mainly acts on $5HT_{1D}$ serotonin receptors, causing vasoconstriction of intracranial blood vessels and inhibition of release

of pro inflammatory neuropeptides from sensory nerve endings of the trigeminovascular system (Priti Girotra et al., 2014)

iv) Corticosteroids

Oral, IM, or IV corticosteroids are beneficial in treating prolonged migraine attacks and menstrual migraine. However, their use carries the usual risk of steroid side effects(Khalid W. Al-Quliti et al.,2016). Their mechanism of action is not clearly established but it possibly exerts its action on central and peripheral sensitization and thus effects perivascular neurogenic inflammation.(Priti Girotra et al., 2014)

v) Opioids

Opioid like codeine, fentanyl, meperidine, and tramadol are employed in the acute treatment of migraine, but they should be kept as a last resort as they may cause drug dependency or addiction(Khalid W. Al-Quliti et al.,2016). These act by prostanoid receptor antagonists, block prostacyclin (PGI2) receptors, which induces headache by vasodilation.(Priti Girotra et al., 2014)

vi) Antiemetics

Antiemetic medications should be used for patients who complain of disabling nausea and vomiting. Several antiemetics are available for use in migraine. Promethazine is effective but sedating, while ondansetron is not. Prochlorperazine has extrapyramidal side effects. Metoclopramide is generally well tolerated and commonly used (Khalid W. Al-Quliti et al.,2016) and they centrally act on dopaminergic pathways(Priti Girotra et al., 2014)

Drug delivery for management of migraine

Few frustrations in medicine can match that felt by the neurologist who holds a potent drug within inches of an infection or a brain tumour it cannot reach. The brain alone among the organs of the body remains inaccessible to chemotherapy. Although the walls of blood vessels elsewhere in the body are fenestrated, they offer free passage, whereas those of the brain are ‘sealed off’. Basically, the so-called blood–brain barrier (BBB) offers free passage to glucose and a few other selected substances but fends of most drugs. Circulating catecholamines, indoleamines, peptides, inter alia, can when present in the CNS, act via specific receptors; their free access to the neurons would have destroyed the specificity of the CNS. In support, all animals with a CNS have a BBB, illustrating the importance of the BBB for higher function. Research in headache disorders has for many decades touched the interface between the CNS and peripheral nociception, but many questions remain.

BBB function in migraine attack

The BBB may be disturbed in many conditions, such as following:

Neoplastic lesions, hypertensive encephalopathy, inflammation, status epilepticus and stroke. However, there is no persuasive data describing transient opening of the BBB in physiological conditions or in migraine attacks with or without aura. Induced cortical spreading depression in rodents reveals a process that shows similarity to the aura . In animal studies, activation of matrix metalloproteinase (MMPs) following repeated cortical spreading depressions may result in opening of the BBB. Thus, theoretically BBB leakage could be present in migraine with aura. However, the degree of activation necessary for this resembles that seen in stroke. In migraine with aura there is oligaemia but no ischemia during the aura phase and early headache phase. Furthermore, diffusion weighted magnetic resonance images (MRI) examined during the aura phase were normal in one study, indicating that there was no observable ischaemia present during the aura. In familial hemiplegic migraine that is severe and long-standing or in attacks of persistent symptoms , a gadolinium enhancement (indirect sign of enhanced passage) has been observed with MRI(L Edvinsson et al.,2008).

The conventional routes for administration of antimigraine drugs are oral (e.g. naratriptan, zolmitriptan, rizatriptan, sumatriptan, ergotamine, non-steroidal anti-inflammatory drugs, opiates),subcutaneous (e.g. sumatriptan, dihydroergotamine), intramuscular (e.g. dihydroergotamine; antiemetics such as chlorpromazine, metoclopramide, prochlorperazine, opiates (eg-butorphanol, meperidine, methadone), intravenous (e.g. dihydroergotamine, antiemetics such as chlorpromazine, metroclopramide, prochlorperazine), Per rectal (e.g. ergotamine, prochlorperazine, metochlopramide) and intranasal (e.g. sumatriptan, zolmitriptan, dihydroergotamine, butorphanol).

The conventional dosage forms have not succeeded in effectively delivering the drug to the target site in brain. The delivery of the drug for the management of migraine requires it to reach the brain which has an impervious barrier, called blood brain barrier, formed from the endothelial membrane. Hydrophilic drugs and drugs with high molecular weights fail to surpass this barrier. To resolve this problem, nose-to-brain route has allured the attention of many researchers in the past decade. Olfactory and trigeminal nerve systems which begin in the brain and end up

respectively at the olfactory and respiratory neuro epithelium in the nasal cavity are the key to all the required solutions for by-passing the blood brain barrier. These systems present a non-invasive drug delivery to brain as these are the only portions of central nervous system which are exposed externally. This route offers high potential for the treatment of migraine, as low concentration of drug is required to effectively reach the target site and achieve a rapid relief. The current research on drug delivery for migraine has also been directed towards the development of novel drug delivery systems such as micro and nano-particulate systems, as the chemical agglomerates of microparticles intended for nasal administration improves flow of powders and are more efficiently delivered at the site(P. Russo et al., 2004).Submicron emulsion is another such novel category for intranasal application as they have been exhibited to possess higher brain targeting efficiency. The submicron emulsion preparation of zolmitriptan was a safe dosage form for rapid and effective intranasal delivery of zolmitriptan (Chaoqun Yu et al., 2011).

The presently available dosage forms administered, for the most commonly prescribed triptans in the treatment of migraine include oral, nasal and subcutaneous routes. Transdermal drug delivery system, particularly iontophoresis, has recently evolved as an alternative for these conventionally available systems. It facilitates controlled and sustained delivery of the active constituent, offers convenient administration and bypasses the first pass metabolism effect (Priti Girotra et al, 2014).

Routes of drug administration to brain

The blood-brain barrier (BBB) has been a great hurdle for brain delivery of anti-migraine drugs. For migraine targeted agents, augmenting brain exposure by increasing blood drug concentrations often is prohibited by systemic toxicity. Therefore, a means for selectively increasing brain exposure, while minimizing systemic exposure, would be desirable.

Carrier Mediated Drug Delivery

Carrier-mediated transport (CMT) and receptor-mediated transport (RMT) pathways are available for certain circulating nutrients or peptides. The availability of these endogenous CMT or RMT pathways means that portals of entry to the brain for circulating drugs are potentially available. In the brain capillary endothelial cells, which make up the BBB, there are several transport systems for nutrients and endogenous compounds. They are (a) the hexose transport system for glucose and mannose, (b) the neutral amino acid transport system for phenylalanine, leucine and other neutral amino acids, (c) the acidic amino acid transport system for glutamate and aspartate, (d) the basic amino acid transport system for arginine and lysine, (e) the b-amino acid transport system for b-alanine and taurine, (f) the monocarboxylic acid transport system for lactate and short-chain fatty acids such as acetate and propionate, (g) the choline transport system for choline and thiamine, (h) the amine transport system for mepyramine, (i) the nucleoside transport system for purine bases such as adenine and guanine, but not pyrimidine bases, and (j) the peptide transport system for small peptides such as enkephalins, thyrotropin-releasing hormone, arginine vasopressin etc . Utilization of differences in the affinity and the maximal transport activity among these transport systems expressed at the BBB is an attractive strategy for controlling the delivery and retention of anti-migraine drugs into the brain (Sandipan Roy,2012).

Olfactory Pathway Mediated Drug Delivery

The possible mechanism by which drugs are transported from nose to brain has not yet clear but olfactory pathway contributes a vital role. This pathway consists of olfactory epithelium, lamina propria and olfactory bulb. Olfactory epithelium contains three types of cells; neuronal cell, progenitor cells and supporting cells, and all are connected by tight junctions. Neuronal cells start from olfactory bulb in CNS to olfactory epithelium in nasal cavity and provide information to brain. Basal cells and neural cells replace each other during their constant motion and due to this constant motion and replacement nasal mucosa becomes permeable resulting in enhanced delivery of drug to brain. Nasal epithelium protects the brain from entry of harmful substances which are entrapped by the mucus layer on epithelium and cleared by cilia. Lamina propria lying on nasal epithelium has blood vessels, mucus secreting glands, olfactory axons and maxillary branch of trigeminal nerve .Olfactory axons are separated into group of 20's and are surrounded by the sheath of Schwann cells restricting perineural transport by decreasing space between axons. This feature of ensheathing the axons is called filia olfactoria . Olfactory bulb is projected to different regions of brain such as piri form cortex, amygdale and hypothalamus, thus helpful for direct nasal delivery of drugs to brain (Mengrui Liu et al., 2017)

In recent studies, intranasal administration of wheat germ agglutinin horseradish peroxidase resulted in a mean olfactory bulb concentration in the nanomolar range. In theory, this strategy could be effective in the delivery of therapeutic proteins such as brain-delivered neurotropic factor (BDNF) to the olfactory

bulb as a treatment for Alzheimer's disease. Recent evidence of direct nose-to-brain transport and direct access to CSF of three neuropeptides bypassing the bloodstream has been shown in human trials, despite the inherent difficulties in delivery . The difficulties that have to be overcome include an enzymatically active, low pH nasal epithelium, the possibility of mucosal irritation or the possibility of large variability caused by nasal pathology, such as common cold. An obvious advantage of this method is that it is noninvasive relative to other strategies (Sandipan Roy, 2012).

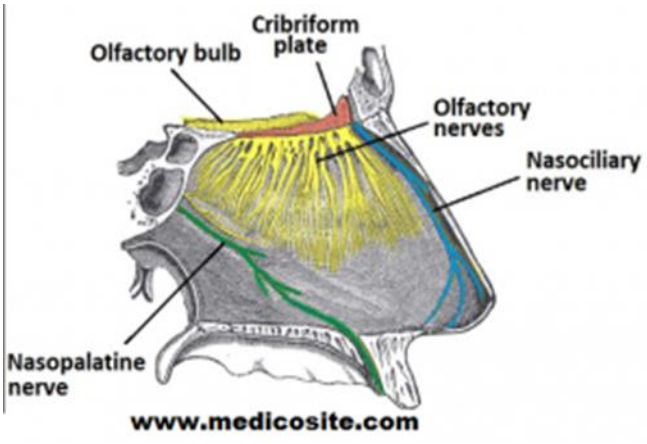

Figure 3. Olfactory pathway

Trigeminal Pathway Mediated Drug Delivery

Trigeminal pathway also plays an important role in intra nasal delivery of drug. Respiratory region occupies major portion of nasal cavity and innervated by trigeminal nerves. Trigeminal nerve is fifth (V) cranial nerve having three branches; ophthalmic nerve, maxillary nerve and mandibular nerve and is responsible for sensation in nasal cavity. Ophthalmic and maxillary nerves innervate the nasal mucosa and carry the necessary information from nasal cavity to CNS. Various drug delivery systems target these two branches for transport of drug to different parts of brain . Trigeminal nerve innervating nasal cavity enters to brainstem through pons, whereas it enters to forebrain through cribriform plate, thus promoting the entrance of drug to caudal and rostral parts of brain and are main focus for IN transport of drugs to brain. Olfactory pathway delivers drug to rostal area of brain, whereas trigeminal pathway not only targets rostal but also caudal area of brain, making it difficult to differentiate whether intranasally administered drug is translocated to rostal area by olfactory or trigeminal pathway . As a result, when drug is intranasally administered to brain, it may be transported via olfactory or trigeminal pathway as depicted in fig (Chandrakantsing Vijaysing Pardeshi,2013)

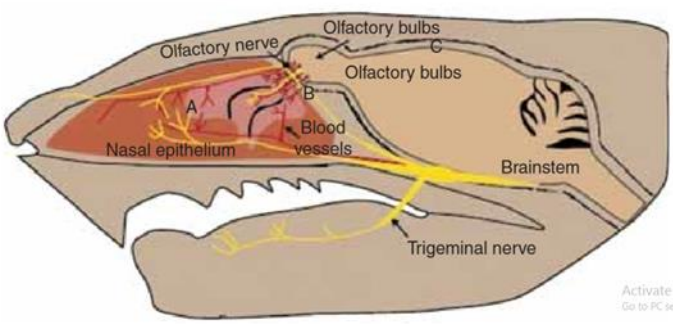

Figure 4. Trigeminal pathway

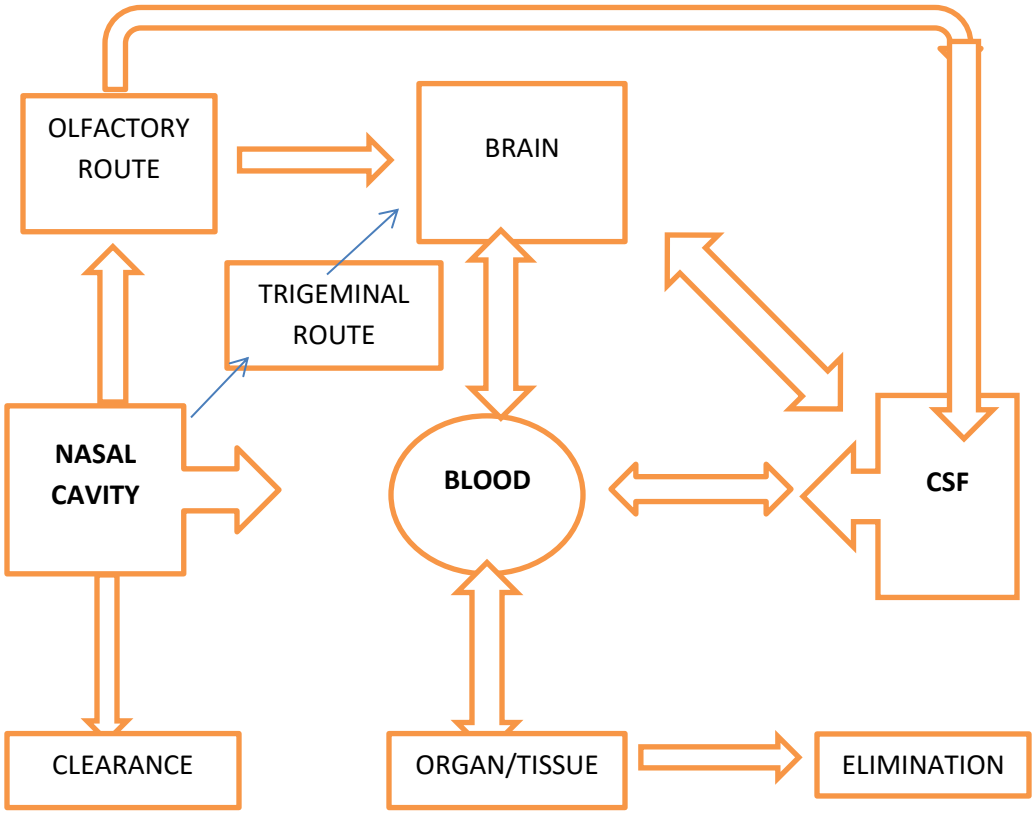

Figure 5. Pathways Of Nasal Drug Delivery for administration of anti-migraine drugs (Chandrakantsing Vijaysing Pardeshi et al.,2013)

Topical Regional Neuro-Affective Mediated Drug Delivery

A method of treating a disease state or condition in humans via topical brainstem afferent stimulation therapy via the administration of a drug to the back of the neck of a human patient at the hairline in close proximity to and under or on the area of skin above the brain stem to provide regional neuro affective therapy is having potential (Ronald Aung-Din,2013).

TRNA has direct effect on CNS through free nerve endings and peripheral nerve connections. They do not rely on dermal, systemic or cerebral blood flow for effect. This system has rapid and prolonged drug effects as regional administration allows high tissue saturation of drug. Side effects are minimized, drug-drug interaction and metabolism/excretion are negligible since drug does not enter the systemic and cerebral blood where as in systemic drug delivery the pharmacological action of drug depends on the drug

levels at CNS target sites, and also the action depends upon the GI absorption, hepatic first pass metabolism, cardiac output and cerebral blood flow.

TRNA differs from the transdermal patch although both are applied to the skin, TRNA triptan therapy offers from the systemic transdermal patch in that topically applied TRNA drug need only traverse the stratum corneum of the skin to reach cutaneous free nerve-endings for therapeutic effect. In contrast, the transdermal patch requires a drug concentration gradient for active drug to enter blood vessels in the subcutaneous tissue and dermis. These are at relative greater distance from the skin surface than the free nerve-endings. Further, after entry into the bloodstream, drug is required to be transported to brain through cardiac output. As active drug is found in both systemic and cerebral blood, drug effect is not isolated to areas of migraine pathology, and extraneous effects are encountered. In contrast, in TRNA therapy, specific TNS(Trigeminal Nerve Stimulation) pathways are affected through afferent neural connections from cutaneous free nerve endings and upper cervical nerve roots. As therapeutic response its determined by rate of neural impulse than blood flow, clinical benefit is realized more rapidly with TRNA triptan delivery.

The analogy is of an electrical capacitor discharging after charge build –up (TRNA) compared to a fluid reservoir filling to a required therapeutic level (transdermal patch). Finally, with TRNA therapy, the specific placement of active drug, as acute use single dose cream or sustained delivery patch, at the BONATH(the back of neck below the hairline) is key in capitalizing on the unique relationship of the region to TNS with respect to providing important different input. On the other hand the systemic transdermal patch may be placed anywhere on the body as anatomical location is irrelavent to its mechanism of action. As dilution in blood is not a consideration with topical regional delivery, active drug dose requirement are also much lower.

As alluded, the principle of TRNA therapy may also be applied to a sustained released patch and other depot drug delivery systems administered to BONATH, with the only requirement of availing active drug to the cutaneous free nerve ending for therapeutic effect. Conditions characterized by persistent, recurrent headaches, such as menstrual migraine, would benefit from such applications.

TRNA technology may be considered environmentally friendly or green. With negligible to no active drug in blood, there is lack of metabolism and excretion into the environment. Likewise, there is no concerns for drug-drug interactions with concomitant medications.

Migraderm is a patented Topical Regional Neuro-Affective (TRNA) migraine therapy. It was developed as an alternative to systemic delivery medications. Migraderm comes in a cream that is applied directly on the skin. Migr is applied on the back of the neck below the hairline. Once applied, it is thought that the neurochemical effect begins to alter impulses to the Central Nervous System (CNS) through free nerve-endings and peripheral nerve connections (Aung-Din R,2012). This could be applied to other triptans as well.

CONCLUSION:

Drug delivery across the BBB is a major limitation in the treatment of migraine disorders. Several pharmacological strategies, possible channels for drug delivery through the BBB, have been described with different levels of success for the delivery of anti-migraine drugs. The above mentioned strategies of drug delivery could form the basis of non-invasive therapy for development of efficient treatment modalities relief of migraine.

Acknowledgements

I would like to thank the principal and management of Al-Ameen College Of Pharmacy, Bangalore and sincere thanks to my guide Dr. V Kusum Devi Mam for her constant support.

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