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A Brief Review on Migraine

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ABSTRACT:

Migraine is a complex disorder presents with one sided headache and nausea type feeling. It can be with aura or without aura. There are several factors, activities or lifestyle modifications considered as triggers for migraine. Timing gap between two meals, in sufficient sleep and stress are amongst the major triggers in migraine. Migraine impacted the quality of life of patient too with repetitive frequency of attack. Based on type and frequency and intensity preventive measures are also available. Extensive research has been done in treatment for migraine attack. Conceptual correlation various cellular and molecular changes and its reflection on various body parts, advancement in treatment has already impacted the globe. Understanding newer aspects in migraine and its complications prepares populations to become more proactive and do avoid possible and probable triggers. This review work prepared with an objective to make medical undergraduates better understand the various theories of migraine and attempt to provide insight knowledge for development of safer and effective novel treatment in migraine.

KEY WORDS: Migraine, CGRP, Aura, headache, nausea

INTRODUCTION

Migraine is a complex disorder presents with one sided headache and nausea type feeling. It can be with aura or without aura. There are several factors or activities, or lifestyle modifications considered as triggers for migraine. Timing gap between two meals, in sufficient sleep and stress are amongst the major triggers in migraine. Migraine impacted the quality of life of patient too with repetitive frequency of attack. Based on type and frequency and intensity preventive measures are also available. Extensive research has been done in treatment for migraine attack. Understanding newer aspects in migraine and its complications prepares populations to become more proactive and do avoid possible and probable triggers. [1,2]

2. PATHOPHYSIOLOGY: The pathophysiology of migraine is complex and unclear though some studies suggest that low level of 5-HT is responsible for activation of Cortical spreading depression (CSD) which leads to activation of Trigeminovasuclar pathway which causes migraine.

Serotonergic pathway: Serotonin has been linked in the pathophysiology of migraine in a number of investigations.[3] It has been discovered that migraine attacks are linked to low serotonin levels (5-HT). Although the mechanism underlying this association is yet unknown, it is probable that changes in cortical excitability or susceptibility of the trigeminal system are responsible.[4]Previous research mentioned that cortical spreading depression was induced by a low 5-HT state, which favors activation of the trigeminovascular nociceptive pathway.[5]one of the investigations found that in the low 5-HT condition, CSD development and CSD-evoked trigeminal nociception were enhanced.[4]The pattern of CSD change found in this study in association with decreased 5-HT is remarkable. The presence of an elevated AUC could indicate that the repolarization mechanism is disrupted in the 5-HT deficient situation. This can result in an increase in cortical excitability as a result. It is well known that different receptor subtypes of 5-HT have different modulatory effects on cortical neurons. In general, 5-HT1 receptor activation has an inhibitory

impact, whereas 5-HT2 receptor stimulation causes cortical activity. [6]As a result, decreased 5-HT1 receptor activation or increased 5-HT2 receptor activation could have resulted in higher cortical excitability in the low 5-HT group. It was previously demonstrated that the 5-HT2A receptor was upregulated in circumstances with low 5-HT, such as migraine patients who overuse analgesics and experimental rats who were persistently given acetaminophen. These findings suggest that the density of 5-HT and 5-HT2 receptors is inversely related. According to this theory, 5-HT depletion causes an up-regulation of 5-HT2 receptors, which leads to an increase in cortical excitability. It is worth noting that 5-HT depletion has a knock-on effect on other neurotransmitter systems like dopamine, norepinephrine, and GABA. As a result, the presence of other transmitters in this process cannot be ruled out.[4]

Cortical spreading depression: Cortical spreading depression (CSD) is a slowly propagating wave of depolarization/excitation followed by hyperpolarization/inhibition in cortical neurons and glia, resulting in a decrease in spontaneous cortical activity, according to some clinical and preclinical investigations.[7,8]During CSD, increased blood flow is followed by decreased perfusion, resulting in a wave of neuronal and glial depolarization and long-term suppression of neural activity.[6]It is characterized by a slow-moving wave of intense neuronal depolarization (2-3 mm/min) that causes a transient spike in cortical electrical activity (on the order of seconds), followed by a long-lasting reduction of electrical activity. Depolarization is associated with an initial posterior hyperemic phase, which is followed by neural suppression and reduced cortical blood flow (30 minutes to 6 hours), which moves anteriorly at 2-3 mm/min throughout the cortex. The rate of advancement of spreading oligemia is identical to that of cortical spreading depression, implying that CSD was the cause of the aura. Because it originates in a clinically silent area of the cerebral cortex, CSD is likely to occur in MO patients and produce headache without causing prior aura signs.[9]Figure depicts the sequence of events highlighting the involvement of CSD, its initiation and propagation, and the pain phase (as experienced during a migraine attack). CSD is initiated mostly in the occipital brain in migraine patients with aura.[6]

The initial membrane depolarization in the cortex mentioned in figure-1 is linked with a substantial efflux of potassium and hydrogen ion, influx of sodium and calcium, as well as other agents such as arachidonic acid and nitric oxide into the neocortex's extracellular space.[6,8]

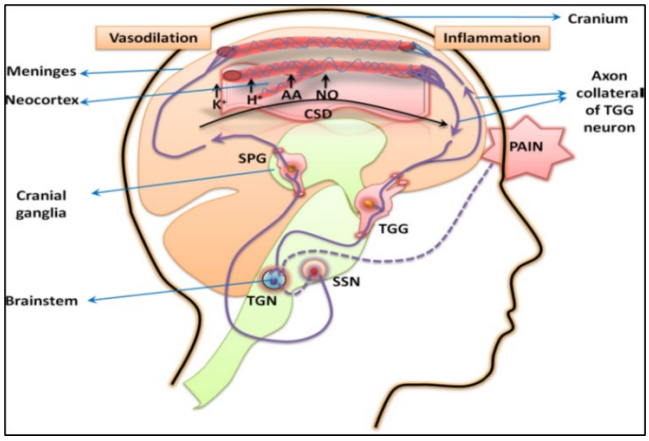

Figure 1 Initiation and propogation of CSD[4]

A self-propagating CSD wave is generated after these agents are elevated to a critical threshold (for example, in the case of K+, the threshold is 10–12 nM), and it progressively advances through the cortex at a modest pace of 3–5 mm/min.[6]Neuronal swelling, dendritic beading, and a decrease in extracellular space are all caused by these ionic alterations. Despite the fact that astrocytes and glia are known to have a role in CSD, their cell volume remains constant. [7] Swelling and dendritic beading inside neurons result in the release of amino acids and neurotransmitters, which propagate the spread of depolarization. One of these excitatory neurotransmitters implicated in the start and dissemination of CSD has been identified as glutamate. Sustained depolarization may be caused by glutamate release and activation of N-methyl-D-aspartic acid (NMDA) receptors. As glutamate levels rise, the generation of nitric oxide (NO) and arachidonic acid metabolites rises as well.[7] Vasodilation and an increase in regional cerebral blood flow are caused by the depolarization wave, which is known as spreading hyperemia. This surge in blood flow lasts around 1–2 minutes, which is slightly longer than the initial CSD event, and is followed by a 1–2 hour period of hypoperfusion. This is referred to as spreading oligemia. These alterations in cerebral blood flow and oxygenation, as well as the higher metabolic demands associated with CSD, because a supply-demand mismatch and normal cerebrovascular homeostasis mechanisms are overwhelmed. Ischemia progression has been linked to variations in blood flow. Animal studies have shown that a single CSD incident is enough to cause a significant reduction in blood supply to the dura. Activation of neurons in the trigeminal ganglia (TG) has been linked to changes in blood flow to the

meninges. CSD has been shown to activate the TG in a number of recent investigations. As a result, there are several lines of evidence pointing to CSD significance in migraine etiology mentioned in figure-2.[7]

Trigeminovascular pathway: In terms of cerebrovascular physiologic impacts, the trigeminocerebrovascular system has a unique and pivotal position. The trigeminovascular system is made up of neurons that innervate the cerebral vessels and have their cell bodies in the trigeminal ganglion. Bipolar cells, the peripheral fiber that makes a synaptic connection with the vessel, and other cranial structures, including the pain-producing large cranial vessels and dura mater, as well as the centrally projecting fiber synapsing in the caudal brain stem or high cervical cord, are all found in the ganglion. The C2 and C3 dorsal roots, which also synapse with the central trigeminal neurons, innervate the more caudal vessels, whereas the trigeminal innervation is largely to the forebrain but extends posteriorly to the rostral basilar artery. Both cerebral (MCA) and extracerebral (middle meningeal artery) arteries are involved in some of the projections.[10]There is evidence to support the hypothesis that CSD is an underlying physiologic process that could contribute to trigeminal nerve activation in migraine.[11]The neurogenic theory is based on the tenet that neural events such as neuronal dysfunction and a phenomenon similar to CSD are responsible for occipital lobe dysfunction, which results in nociceptive afferent activation and dilation of blood vessels on the dura, triggering trigeminal nerve activation.[6]The ophthalmic branch (V1) supplies the majority of the cranial dura mater nerve fibres, whereas collaterals from the maxillary branch (V2), mandibular branch (V3), and cervical root ganglion supply dural innervation to smaller caudal regions. This nociceptive information is carried into the brainstem by afferents from the TG, which mostly terminate at second order neurons in the trigeminocervical complex (TCC). [12]The release of CGRP is enhanced when trigeminal neurons are activated. CGRP, along with substance P and neurokinin A, has a role in mediating neurogenic inflammation, which includes vasodilation, plasma protein extravasation, and mast cell degranulation.[13]

Calcitonin gene related peptide (CGRP): Calcitonin gene-related peptide (CGRP) is a 37-amino-acid regulatory neuropeptide produced from the calcitonin/CGRP gene by alternative splicing.[13] CGRP is the most potent vasodilatory neuropeptide known, and it's thought to play a role in a number of pathophysiological processes, including dilation of cerebral and dural blood vessels, release of inflammatory mediators from mast cells, and transmission of nociceptive information from intracranial blood vessels to the nervous system.[13,14]CGRP is thought to have a crucial role in the painful phase of migraine based on these findings mentioned in figure-3.[13] In migraine, neurogenic inflammation is thought to increase CGRP release. The effect of an inflammatory cocktail containing bradykinin, histamine, serotonin, and prostaglandin E2—agents that drive neurogenic inflammation—on CGRP release in cultured trigeminal neurons of Sprague-Dawley rats was investigated in vitro. In order to mimic neurogenic inflammation, the neurons were treated with an inflammatory cocktail that resulted in an increase in CGRP release that was at least as large as that caused by potassium chloride or capsaicin. The discovery that trigeminal ganglion neurons release CGRP in conditions that simulate neurogenic inflammation supports the theory that CGRP plays a function in migraine. Increased CGRP synthesis and release could be mediated by MAPK pathway activation, which can be influenced by endogenous inflammatory chemicals like TNF-α. TNF-α-1 receptors were found on the majority of CGRP-containing rat trigeminal ganglion neurons, according to the research.[14]

Retinal migraine: The ophthalmopathological condition, retinal migraine is defined as a temporary monocular scotoma or visual loss that is accompanied or followed by a headache.[15] The visual loss is usually shorter than the migraine-associated aura, lasting less than 5 minutes but up to 30 minutes, the longest ocular migraine episode recorded was 7 hours, and the patient recovered completely. Although there is a high family history of migraine and ocular migraine, no unambiguous inheritance patterns have been identified. Calcium channel mutations have recently been discovered in patients suffering from familial hemiplegic migraine. Increased endothelin-1, a potent vasoconstrictor whose levels have been demonstrated to be higher during and between migraine episodes, could also be a risk factor. Endothelin-1 has showed considerable variation for a receptor identified to induce vasoconstriction in migraine patients.[16] The pathogenesis of chronic visual auras is unknown; however it could be related to hyperexcitability of the N-methyl-D-aspartate (NMDA) receptor or central inhibitory dysfunction.[17] A relationship between migraine aura and CSD has been demonstrated in several recent investigations using magneto-encephalography, or high-field intensity, high-resolution magnetic resonance

imaging. During migraine visual aura, for example, CSD generates a retinotopic visual percept as it propagates inside the human primary visual cortex.[17]Repeated occurrences of reversible monocular visual disturbance, including scintillations or blindness, which appear gradually over 5 minutes and persist 5 to 60 minutes are referred to as retinal migraine. When patients are assessed acutely during an episode, reversible vasospasm is rarely recorded. Calcium channel blockers can be used as a preventative measure. [15]

Migraine overcomes by vomiting: Migraine is usually associated with nausea and vomiting; nevertheless. The pain-relieving ability of vomiting during migraine attacks has been noted by several migraineurs as an interesting phenomenon. Hundreds of online patient forums detail experiences of the participants with migraine attacks improving or disappearing after vomiting.[18]Toxins, drugs, bacteria, viruses, and fungi that enter the gastrointestinal lumen and, as a result, indirectly stimulate the brainstem emetic nuclei located within the dorsal vagal complex via release of local emetic neurotransmitters within the upper alimentary canal and subsequent activation of corresponding receptors on vagus nerves can cause nausea and vomiting.[19]The enteric nervous system, the interstitial cells of Cajal, fibroblast-like cells, gastric smooth muscle, the CNS, and therefore the ANS all work together to regulate digestion under normal conditions. The vagus nerve transmits afferent sensory information from the GI tract to the brainstem's nucleus tractus solitarius (NTS), which ultimately leads to efferent sympathetic or parasympathetic innervation of the GI tract, which modulates GI function by lowering or enhancing GI secretion and motility.[20]Enterochromaffin cells synthesize >90% of the body's 5-hydroxytryptamine (serotonin, 5-HT) and substantial amounts of substance P (SP) in the gastrointestinal tract, which are both essential for gastrointestinal motility, nausea, and vomiting. Enterochromaffin cells release 5-HT and/or SP in a calcium (Ca2+)-dependent manner in response to chemical, mechanical, or neurological emetogenic stimuli. 5-HT, CGRP, and most likely SP stimulate their emetic receptors (serotonin 5-HT3 and substance P neurokinin NK1 receptors, respectively) on the vagal afferents, causing nausea and vomiting.[20,21]The activation of serotonin 5-HT3 receptors on vagal afferents by serotonin released by enterochromaffin cells in the gastrointestinal tract plays a significant role in the start of vomiting.[22]Peristaltic and secretory reflexes are triggered by serotonin acting on 5-HT1P receptors, while 5-HT4 receptor stimulation increases neurotransmitter release in reflex pathways. Blocking 5-HT3 receptor activity can slow intestinal motility, whereas activating 5-HT3 receptors on visceral afferent fibers can cause emesis. Inflammation also causes a reduction in serotonergic signaling in the mucosa. Increased stomach accommodation and improvement in postprandial symptoms in patients with functional dyspepsia, as well as improvements in common gastroparetic symptoms such as nausea and vomiting in patients with gastroparesis, have been found in studies examining the effects of 5-HT1A agonists. α-CGRP and β-CGRP are CGRP isoforms that are mainly expressed in sensory and enteric neurons, respectively, and have been demonstrated to innervate a range of digestive system locations. Changes in the intestinal microbiota and gut permeability in reaction to stress events, as well as the release of CGRP from parasympathetic perivascular and trigeminal fibers in migraine, can contribute to the release of proinflammatory mediators. As a result, nociceptive responses in the trigeminal pathway can be affected, leading to migraine onset.[20] Stimulation of cervical, thoracic, or cardiac vagal afferents suppresses second-order nociceptive neurons in the trigeminal nuclear complex and the spinothalamic and spin reticular tracts of the spinal cord.[23]Thus by the suppression of Trigeminal nuclear complex pain perception is stopped and which can lead to stop migraine pain.

SYMPTOMS: [28]

- Sensory sensitivities and Neck stiffness.
- Photophobia
- Phonophobia
- Osmophobia
- Allodynia
- Nasal stuffiness and flushing
- Yawning
- Mood change and fatigue
- Nausea and vomiting
- Vertigo

TREATMENT: For acute migraine treatment, a variety of treatment options are available, including 5-HT1B/1D agonists, nonsteroidal anti-inflammatory medications (NSAIDs), and steroids. β- Blockers, calcium channel blockers, CGRP antagonist and anti-epileptics are commonly used as prophylaxis in chronic attacks. Riboflavin and vitamin B12 and other nutraceutical formulations are available that can aid with migraines.[29, 30]

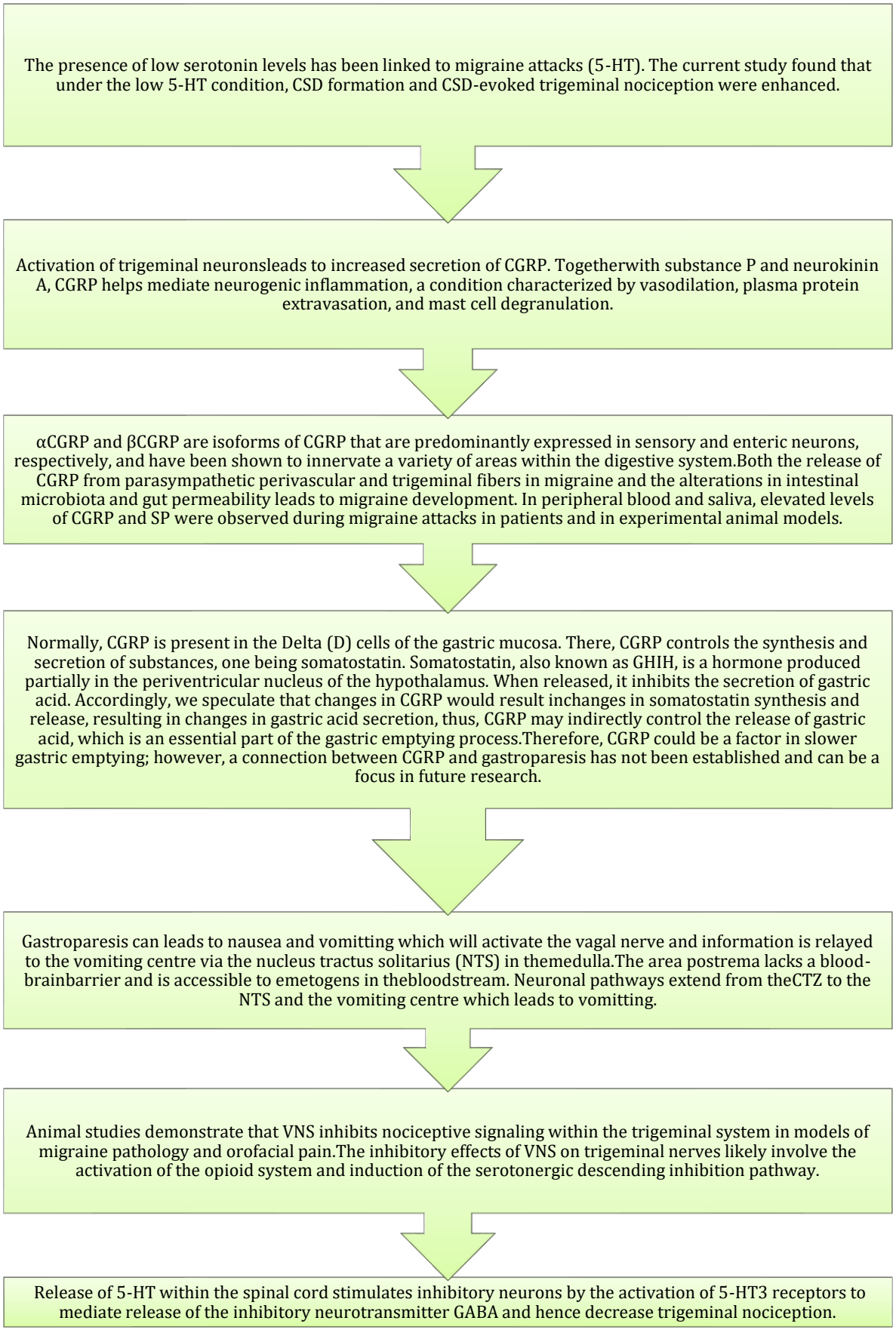

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Figure 2 Pathophysiology part-I (9,13,20,24–26)

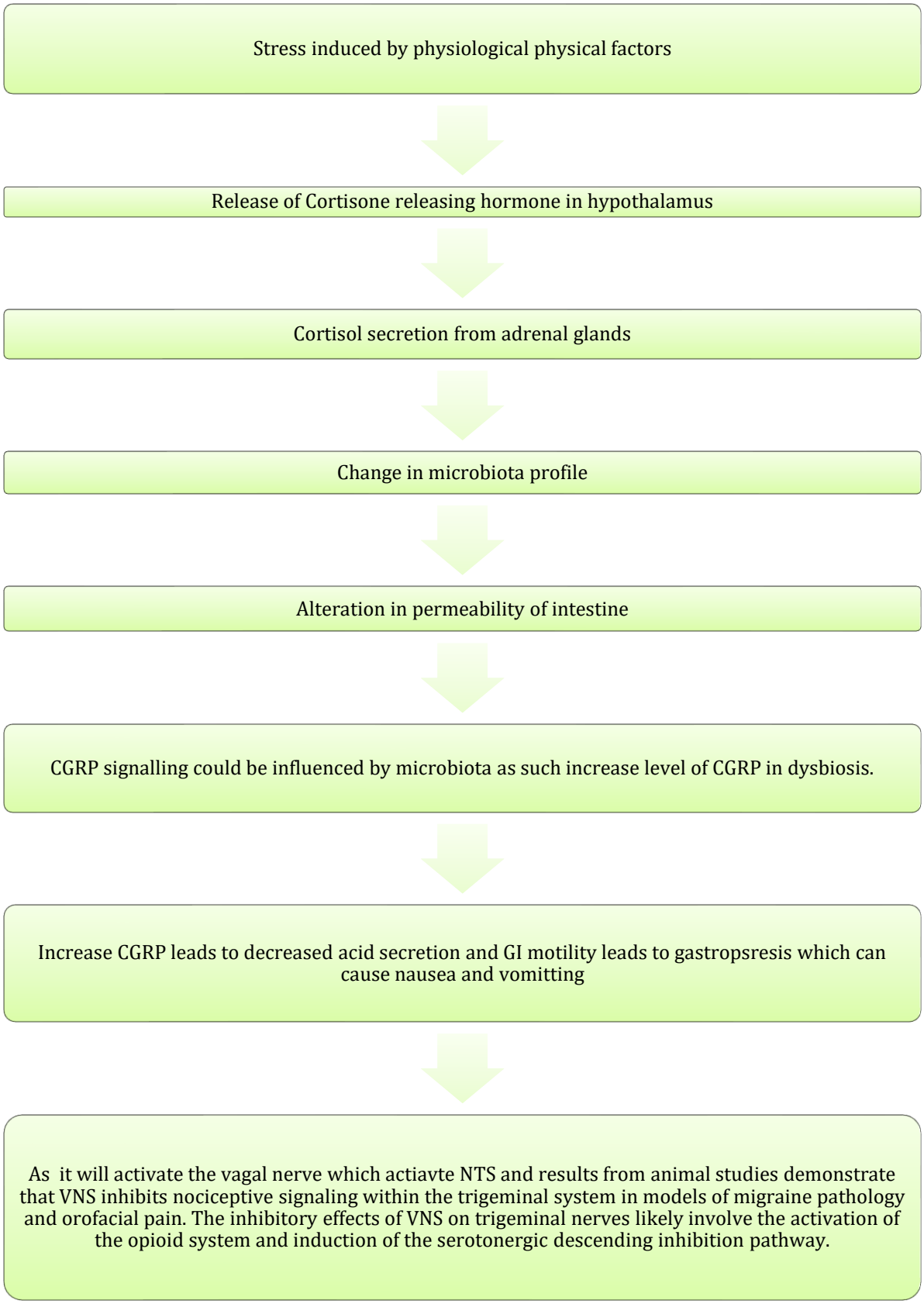

Figure 3 Pathophysiology part-II (25,27)

CONCLUSION

Extensive research has already been done in migraine pathogenesis provides opportunity for designing preventive measures in last decade. Understanding various possible mechanisms in understanding of migraine offers more spectrums in designing better therapeutic approach in future. Probable triggers associated with mechanism can also be avoided based on proper understanding.

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