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Marvi S. Qureshi

University of Central Florida, marvisq358@knights.ucf.edu

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Analysis of the Pathomechanism and Treatment of Migraines Related to the Role of the Neuropeptide CGRP

By: Marvi S. Qureshi

Faculty Mentor: Dr. Mohtashem Samsam

UCF Burnett School of Biomedical Sciences

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ABSTRACT: Migraines are a type of headache that specifically act on only one side of the head, although about 30% of patients with migraines may experience a bilateral headache. Migraines are brain disorders that typically involve issues of sensory processing taking place in the brainstem. Possible causation has been linked to blood vessels, blood flow, and oxygen levels in the brain. Migraines can be described in three phases, all of which have a common neuropeptide known as the calcitonin gene related peptide (CGRP). CGRP increases in plasma have been linked to migraine headaches, and specific treatment plans have been tailored to account for this. CGRP is a vasodilator that causes dilation of cranial blood vessels and can lead to possible neurogenic inflammation in the periphery of its release while activating the pain pathway in the brainstem. The primary treatment for migraines is currently drugs from the triptan family and NSAIDs, as well as prophylactic drugs including antiepileptic drugs, beta-blockers, and Ca²⁺ channel blockers. This literature review will expand on this information regarding migraines, specifically discussing the pathophysiology, treatment, and CGRP relation to migraines through a summary of the compilation of various studies conducted. Through this literature review, it will then become apparent as to what research should be conducted to further the field of study on migraines based on what related topics have not been currently explored in depth in other studies.

KEYWORDS: Migraine, Migraine Onset, CGRP, Nerve Fiber Vasodilation, Migraine Treatment Plan, Inflammation

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INTRODUCTION

In general, migraines are a specific type of headache that involve a unilateral pulsing pain. This pain typically affects only one side of the head, although about 30% of patients may experience a bilateral headache¹. Migraines have been found to last from four to 72 hours. Common symptoms associated with this pain include nausea, disturbed vision, vomiting, photophobia (hypersensitivity to light), and phonophobia (hypersensitivity to sound)¹. Migraines are split into two different classes: the common and classic migraine. The majority of migraines are classified as common migraine. In addition, migraines can be described as having or lacking aura, which are neurological disturbances that are visual, motor, and sensory². Common migraines are not typically accompanied with aura. The classic migraine comprises around 15% of total migraines and is thus the minority class of migraines¹.

Migraines are typically caused by issues in the cerebral blood vessel walls, impairment in blood flow (that could be due to severe vessel contraction), abnormal platelet numbers, varying brain oxygenation, or varying metabolism levels². Migraines can be caused in response to a single or combined effect of all of these issues, and vary depending on the specific case of migraine displayed and on the individual displaying it. However, in most cases, migraines have been found to involve blood vessels, either intracranial or extracranial, as well as information communicated by the sensory nerve fibers to the central nervous system². Studies conducted through positron emission tomography (PET) have indicated that the activation of the brainstem and brain is involved in initiating migraines and that this activation is constant both with and without aura³. In this literature review, information from a variety of studies will be analyzed and discussed regarding the pathophysiology, treatment, and CGRP effects of migraines. Afterwards, these experiments will be summarized to discuss future research that should take place to make further progress in this field.

CALCITONIN GENE RELATED PEPTIDE

CGRP is an important 37 amino acid neuropeptide that was discovered using RNA transcripts²⁶. These transcripts are from the calcitonin gene and alternative processing leads to different mRNAs that encode the hormone calcitonin²⁷. CGRP plays an important role in the primary sensory neurons in which it is localized,

specifically through the activation of the trigeminal system²⁹. Its associated areas of action have a wide distribution from the peripheral skin, cornea, respiratory, and urogenital systems to the terminals close to smooth muscle. CGRP-containing neurons and fibers are also found in autonomic ganglia and in parts of the central nervous system and in the cerebral dura²⁹.

Activation of the trigeminal system as well as tissue stimulation and/or tissue injury causes the release of CGRP from the brainstem trigeminal nucleus and spinal cord. Cranial vasodilation, coupled with the activation and sensitization of sensory nerves, has been suggested by several studies to lead to the headache phase²⁹. CGRP is a vasodilator of the cranial vessels that causes the nerve endings to be disturbed and the nerves to be pinched. This, in turn, causes more vasoactive material to be released, such as CGRP, producing a vicious cycle and resulting in neurogenic inflammation. The method of action has been found to be related to CGRP blocking the release of aldosterone secretion as well as promoting the release of catecholamine, which is done through CGRP Type 1 receptors. This action leads to the vasodilation effect that is associated with CGRP²⁷.

CGRP has also been found to enhance the activity of another neuropeptide, Substance P (SP), when they are both co-administered in the CNS. This enhanced activity has been suggested due to CGRP's ability to inhibit an enzyme directly involved in SP degradation²⁹. SP has also been linked to excitation of the neuronal network, where CGRP is believed to control SP degradation. Thus, CGRP release has been shown to have correlations with the duration and intensity of painful stimuli.

CGRP receptors have been found to contain proteins (RAMPs, or receptor activity modifying proteins) that must be present to move the receptor to the membrane of the cell. There are various forms of RAMP: RAMP1, the form of RAMP that is specifically involved with CGRP, moves the functional glycoprotein receptor to the membrane surface to act as a receptor for CGRP³⁰. This glycoprotein in humans is the rate-limiting factor for the release of CGRP in neurons³¹.

Previously, CGRP receptors were separated into two CGRP receptor types, however, as of now, experiments have confirmed that there is only one CGRP receptor, which is the CGRP1 receptor. There are many components of a CGRP receptor, which include a transmembrane domain for a receptor activity modifying protein type 1

(RAMP1), a G protein coupled receptor, and a receptor component protein (RCP)³². All of these components are necessary to form a working CGRP receptor. It has been determined that the first seven amino acids on the N-terminal end of the CGRP receptor are necessary to lead to the activation of the receptor, and as such various CGRP receptor antagonists are involved with this end of the protein³².

CGRP receptors can be found in many different locations in many different types of cells, and are not just limited to the cardiovascular and nervous system. CGRP receptors are on glia and neurons in the central nervous system, as well as on many second order neurons, in addition to mast cells that are present inside the dura mater³². Various antimigraine treatments act on CGRP release through involvement of CGRP receptors. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), for example, block the release of CGRP that is promoted through the activation of the prostaglandin receptor. By contrast, neuronal 5HT receptors are activated by triptans, which lead to the blockage of CGRP release³³.

Dural surface electrical stimulation has led to a release of CGRP from trigeminal afferents. This release leads to vasodilation and an increase of the meningeal blood flow. Nitric oxide (NO) has a synergistic effect along with CGRP on the blood flow, and this theory has been proposed to explain the NO-mediated facilitation of CGRP synthesis and release in the trigeminal ganglia neurons³⁴. CGRP promoter activity has been increased by overexpression of nitric oxide synthase and NO donors.

Nitric oxide is a vasodilator similar to CGRP that affects the arterial diameter and increases it, which leads to an increase in blood flow throughout the brain, causing a similar role to CGRP in the pathomechanism of a migraine³⁵. In addition, NO increases the production and exocytosis of CGRP, even when the stimulation is electrical³⁴. Accordingly, inhibitors of nitric oxide synthesis prevent CGRP release³⁷.

Sex hormones in females are also important in the synthesis and the eventual expression of the receptor for CGRP²⁶. 17 β -estradiol leads to increased neurogenic vasodilation, and the mechanism through which this takes place is possibly through an increase of CGRP. This is believed to be a method by which 17 β -estradiol exacerbates migraines in females³⁸.

CGRP has also been found with the brain-derived neurotrophic factor (BDNF) in trigeminal neurons, making BDNF a mediator of trigeminal nociceptive plasticity²⁶. BDNF is a neurotrophin that regulates factors such as maintenance, differentiation, and survival of various central and peripheral neurons. When BDNF is in low concentrations, this can lead to excitation of neurons in the hippocampus, cerebellum, and cortex³⁹.

CGRP has also been found to increase plasma protein leakage by various neuropeptides, including SP. The effect of these neuropeptides has been increased by injection of CGRP⁴⁰. It has accordingly been theorized that the co-release of CGRP with these neuropeptides may have additive effects in pain. In addition, CGRP and SP levels have been found to increase salivary secretions of patients suffering from migraines²⁶. Thus, inhibiting the release of these neuropeptides, specifically CGRP, is an important treatment for migraines.

CURRENT TREATMENT OF MIGRAINE

Prophylactic treatments are used to treat acute migraine attack, and are currently used as strategies to treat migraine headaches. Treatment methods include such first-line drugs as triptans and NSAIDs; in addition, anti-epileptic drugs, antidepressants, beta-blockers, and natural supplements are used to treat migraines (Table 1)⁴. Acupuncture, as well as other non-drug treatments, is used as well.

Medications

Drugs are utilized in the asymptomatic phase between acute attacks where no symptoms are observable while in the prophylaxis of a migraine². These drugs include Timolol and Propranolol, which are both beta-blockers. Propranolol has been found to act by inhibiting cortical spreading depression in the aura phase of migraines, and a possible method of action to achieve this inhibition effect has been through the blockage of glutamate release⁴¹. For patients with depression or sleep issues, Amitriptyline, a tricyclic antidepressant, is used⁴⁰. Drugs such as Divalproex, an anticonvulsant, and Verapamil, a calcium channel blocker, are also used².

Acute attack treatment is divided into prodromal phase and headache phase. The prodromal phase is described by aura and neurological symptoms that are experienced prior to the actual headache²⁶. Treatment applied during the prodromal phase is conducted by the Triptan family,

which includes drugs such as Zolmitriptan, Naratriptan, Rizatriptan, Eletriptan, Almotriptan, and Sumatriptan, all of which have been shown to quickly decrease migraine headaches in patients². Sumatriptan is the most widely used antimigraine drug, and is the most effective antimigraine prophylactic drug. This drug brings elevated CGRP back to normal levels and also relieves the headache in studies that have been conducted⁴³. Triptan oral administration inhibits gastrointestinal mobility and thus may not completely relieve pain, and as such various other methods of administration such as nasal spray or subcutaneous injection may provide more effective treatment⁴⁴.

Triptans have been found to be more effective when administered during the headache phase rather than during the aura phase⁴⁵. In fact, the general oral treatment of migraine attacks (as recommended by the European Federation of Neurological Sciences) should take place earlier during the headache phase to prevent incorrect absorption that may take place during the migraine⁴⁶. But if a non-oral administration of triptans is being given, the most effective period to administer the drugs has been found to be just prior to the symptoms of the migraine becoming severe⁴⁸. A side effect of triptan drugs, however, is that they constrict coronary arteries, leading to chest tightness and pain, which can in turn create significant side effects in patients suffering from coronary diseases⁴⁹.

Another drug given during the prodromal phase is the vasoconstrictor Dihydroergotamine, a derivative of ergotamine. This drug should not be used while pregnant or by patients that have coronary artery disease because nausea is a side effect. These triptan drugs have been shown to be effective in most cases⁵⁰.

The headache phase is associated with cerebral vasodilation as well as symptoms that include nausea or vomiting, and analgesics such as non-steroid anti-inflammatory drugs (NSAIDs) are used for treatment²⁶. These symptoms are not specific and act on many different receptors and molecules such as cyclooxygenase and other inflammation-related receptors. Naproxen, meclizolamine, and aspirin are common NSAIDs used for antimigraine treatment⁵⁰. If the pain is severe, opioids, mepreidine, or codeine sulphate can be used to decrease pain. Opiates specifically decrease the calcium influx (pre-synaptic) and increase the potassium efflux (post-synaptic), which then decreases the duration of the action potential by decreasing the positive charge

inside the postsynaptic terminal. Anti-emetic drugs are used to treat nausea, examples of which are domperidone and metoclopramide⁵¹. Medication overuse is lower in patients that are using triptan rather than analgesics, and opioids have been shown to have a lower efficiency at treating migraines overall⁵².

Epilepsy and migraines have similar clinical features, and as such antiepileptic drugs can also be used for antimigraine treatment due to their prevention of the stimulation of the brainstem⁴. Topiramate, gabapentin, and valproate are involved with gamma-aminobutyric acid by increasing the inhibition of GABA. Gabapentin and valproate alter GABA metabolism, leading to its eventual inhibition⁵³. Topiramate also inhibits the action of GABA, but does so by acting on the receptors. In various double-blind trials, the actions of these drugs have been shown to be more positive than a placebo⁵⁴. Topiramate has also been shown to prevent the exocytosis of CGRP and thus prevent vasodilation as well by directly acting on trigeminal sensory nerves⁵⁵.

For a severe migraine attack, the first drugs of choice are sumatriptan administered subcutaneously and acetylsalicylic acid administered intravenously. Steroids can help treat a status migrainosus. Betablockers, topiramate, valproic acid, and flunarizine are the first choice to treat the prophylaxis of migraines. Second choice drugs are bisoprolol, naproxen, pemetidone, and amitriptyline⁵¹.

CONCLUSION

Considering all that has been analyzed in terms of migraines and the relation to CGRP in various studies that have been conducted, it is the author's recommendation that additional CGRP receptor antagonists that are able to decrease the release of CGRP are the most promising avenue, and thus should receive particular attention. This experiment can effectively be conducted through analysis of CGRP effects under typical conditions, analysis of known CGRP receptor antagonists, and analysis of new CGRP receptor antagonists, an area where current research is lacking. In an ideal situation, this experiment would be conducted on ex-vivo dura mater from an animal such as a mouse.

Table 1. Common Medications for Anti-Migraine Treatment⁴

Antimigraine Drug	Class	Action
Propranolol	Beta-Blocker (blocks beta-adrenergic receptors)	Acts in asymptomatic phase between attacks
Timolol		
Amitriptyline	Tricyclic Antidepressant	Acts in asymptomatic phase between attacks, used by patients with depression or sleep issues
Divalproex	Anticonvulsant	Acts in asymptomatic phase between attacks
Verapamil	Calcium Channel Blocker	Acts in asymptomatic phase between attacks
Zolmitriptan	Triptan Family [serotonin receptor (5-HT _{1B/D}) agonists]	Act in prodromal phase. Quickly decrease migraine headache onset. Can also constrict coronary arteries
Naratriptan		
Rizatriptan		
Eletriptan		
Almotriptan		
Sumatriptan		
Dihydroergotamine	Derivative of Ergotamine [acting on serotonin receptor (5-HT _{1B/D}) and other receptors]	Vasoconstrictor
Naproxen	Non-steroid anti-inflammatory drugs (inhibit COX-1 and COX-2)	Used in headache phase and help to deal with symptoms
Meclogenamate		
Aspirin		
Domperidone	Anti-emetic drugs	Used to treat nausea in headache phase
Metoclopramide		
Olccegepant	CGRP receptor antagonist	Block central and peripheral CGRP receptors
Telecegepant		
Valproate	Anti-epileptic drugs (decrease neuronal activity by increasing Cl ⁻ influx, decreasing Ca ⁺⁺ influx, and other mechanisms)	Inhibit activation of brainstem
Topiramate		
Gabapentin		

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