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Honors Thesis Proposal

Exploration of Bioactive Compounds of Ginger as a Folk Remedy for Migraines

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Abstract

Ginger has been reported to alleviate migraine pain. Ginger has four bioactive compounds that have the ability to reduce nitric oxide synthase (NOS) resulting in the inhibition of nitric oxide (NO) causing vasoconstriction. Leading to the hypothesis that ginger has structural similarities to vasoconstrictor drugs causing similar receptor interactions. In order to verify this claim, a structural analysis experiment is proposed in order to determine similarities between ginger and vasoconstrictor drugs.

Introduction

A migraine is a brain disorder that is typically characterized as a moderate to severe throbbing pain with associated symptoms of nausea, vomiting, sensitivity to light (photophobia), sound (phonophobia) and head movements.[1] Migraines affect 12% of the population and result in decreased work productivity and performance. In 2004, the Headache Classification Committee of International Headache Society (IHS) published a paper with a new classification of migraines called 'migraines with aura'. The original migraine definition was kept the same, however 'migraine with aura' was used to define a migraine in which reversible loss of vision, speech symptoms, and sensory symptoms occur.[2]

Migraine History

Not much is known about migraines, however three major theories have been proposed to help understand the mechanism of migraines.

In 1938 Harold Wolff established the first migraine theory known as the vascular theory. Wolff found that patients with migraines had extracranial vasodilation that could be treated by using vasoconstrictors. Wolff concluded that vasodilation results in migraine pain, and vasoconstriction can be used to alleviate the pain.[3] After this finding, DeVries suggested that the vascular pulsation leads to activation of stretch receptors leading to release of neuropeptides such as calcitonin gene-related peptide (CGRP) from perivascular nerves. CGRP is a potent vasodilator, which can lead to migraine pain.[4] Although the vascular theory was initially believed to be the only mechanism of action by which migraines arise, another theory was created which further expands on the pathology of migraine.

In 1983, James W. Lance showed that blood flow changes that occur in migraines can be created by stimulation of the brain stem leading to the formation of the neurogenic theory.[5] In 1993, Moskowitz further supported this theory when he published a paper that demonstrated that inflammation of dural membrane leads to headache pain. Moskowitz noticed that the release of vasopeptides from the trigeminal axons of the dura and pia mater produced an inflammatory reaction with pain.[6] This inflammatory reaction stimulates the trigeminal ganglion causing protein extravasation (protein leakage). The proteins released are vasoactive

peptides such as calcitonin gene-related peptides (CGRP) and substance P.[7] These two vasoactive peptides play key roles in dural inflammation because substance P causes protein extravasation. CGRP works synergistically with substance P by increasing blow flow in the dura and inhibiting metabolism of substance P resulting in dural inflammation and nerving ending irritation.[8] Based on these findings the neurogenic theory demonstrated that vascular changes result in inflammation and dilation of dural membrane causing a migraine.

Two major theories were established that explained the mechanism of migraines, however, these did not account for 'migraine with aura'. This phenomenon was addressed in the neurological theory, which states that 'migraine with aura' is caused by depolarization of cortical neurons from the occipital lobe (back of the head) toward the frontal lobe.[9] Depolarization of the cortical neurons results in sensory or motor impairment leading to loss of vision, speech symptoms, and sensory symptoms.[10] This process is called cortical spreading depression (CSD). CSD is typically coupled with a period of hyperemia (increased blood volume) followed by a period of oligemia (decrease blood volume). Studies suggest that a catalyst of CSD is nitric oxide (NO), a potent vasodilator.[10]

These three theories not only explain the cause of migraines, but also show the relationship between migraines and vasodilation, which is why a majority of migraine medications used are vasoconstrictors. The following literature review will focus on the relationship between migraines and ginger (vasoconstrictor).

Relationship between serotonergic receptors, nitric oxide, and calcitonin gene-related peptide in migraines

The 5-hydroxytryptamine receptor is a serotonin receptor that has been reported to produce or prevent migraines based on whether the ligand activates (agonist) or inactivates the receptor (antagonist).[11] For example, a recent study has shown that when the 5-HT_{2A} receptor is activated its causes pain, inflammation, and vasodilation. Initial interest in this receptor occurred in an experiment where researchers noticed an increase in 5-HT_{2A} (ligand) on a platelet membrane of a migraine patient.[12] This observation had peaked the interest in the relationship between the 5-HT_{2A} receptor and nitric oxide (NO) system. NO is an important factor in the development of migraine due to its ability to cause vasodilation. This was seen in a study in which nitroglycerin (NO donor) caused migraines in non-migraine control patients and more pronounced migraine in patients with existing conditions.[13] The sentence on 'cGMP' was accidently left from editing, I removed it.

In order to determine the relationship between nitric oxide and HT_{2A} receptor, two experiments were carried out. The first experiment determined the effect of 5-HT_{2A} receptor agonist 1,2,5-dimethoxy-4-iodophenyl-2-aminopropane (DOI) on chemical (discomfort pain sensation) and thermal nociception (burning pain). While the second experiment conducted, investigated the effect of DOI on regional cerebral blood flow and NOS (nitric oxide synthase) expression in the trigeminovascular

nerve fibers and neurons. These experiments were run on mice, which would be dissected, and immunohistochemically studied.

The results of these two experiments showed that 5-HT receptor caused cerebral hyperemia (increased blood flow in the brain) and increased nitric oxide synthase (NOS) expression in trigeminal ganglion and trigeminal nucleus caudalia. In addition, researchers found that 5-HT_{2A} receptors activated by DOI caused activation of trigeminovascular NO pathway similarly to mice injected with nitroglycerin (NTG), a nitric oxide donor that causes migraines. DOI activates the NO pathway by increasing NOS cells in the trigeminal nerves. These findings lead to the conclusion that nitric oxide synthesis occurs by activation of the 5-HT_{2A} receptor. The 5-HT_{2A} receptor causes an increase in intracellular calcium resulting in activation of NOS pathway. NOS allows the release of NO from neurons. Once released, NO diffuses back into the presynaptic terminal in order to release neurotransmitters such as substance P and CGRP.[14] These findings suggest a link between NO and CGRP, that has been shown by two studies that demonstrated NO-donor-triggered migraines cause an increase of CGRP even when blocked by sumatriptan.[15-16]

The 5-HT_{2A} receptor is not the only type of serotonin receptor that can cause and suppress migraines. The genes in our body code for different types of serotonin receptors each with a unique mechanism of action and effect on migraines that can as can be seen in Table 1. Some receptors have subclasses with the same effect but are just encoded by different genes. For example, HT_{1A} receptor is encoded by HTR1A gene, while the HT_{1B} receptor is encoded by HTR1B gene.[17-19]

Table 1: Classification of Serotonin Receptors

Receptor	Subclasses	Ligand Type	Mechanism of action	Effect
5-HT$_1$	5-HT$_{1A, B, D, E, F}$	Agonist	Allows the decrease of cyclic adenosine monophosphate (cAMP)	Induces vasoconstriction and reduces inflammation by inhibition of substance (CGRP, substance P, NO) from trigeminal nerve causing redistribution of blood flow resulting in alleviation of migraine pain.
5-HT$_2$	5-HT$_{2A, B, C}$	Antagonist	Allows the increase levels of IP3 and DAG	Prevents increase of intracellular calcium resulting decrease of nitric oxide causing vasoconstriction causing alleviation of migraine pain
5-HT$_3$	N/A	Antagonist	Prevents depolarization of the plasma membrane	Reduce vascular pain caused by inflammation and inhibition of substance (CGRP and substance P from the trigeminal nerve.
5-HT$_4$	N/A	Agonist	Allows increase of cyclic	Intracranial vasoconstriction

			adenosine monophosphate (cAMP)	
5-HT$_7$	N/A	Antagonist	Allow increase of cyclic adenosine monophosphate (cAMP)	Decreases level of CGRP and substance p resulting in vasoconstriction relieving migraine pain

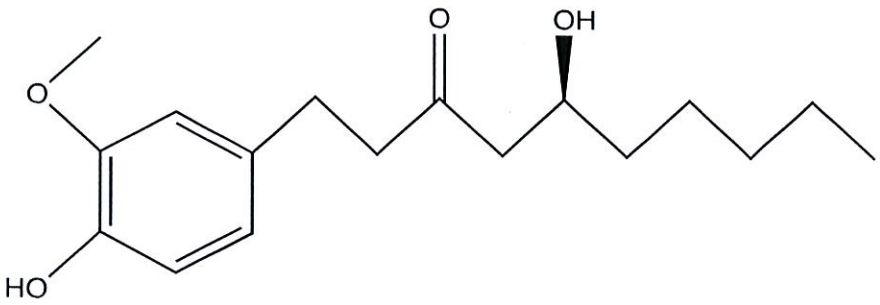
Components of Ginger

Table 2: Species of Ginger

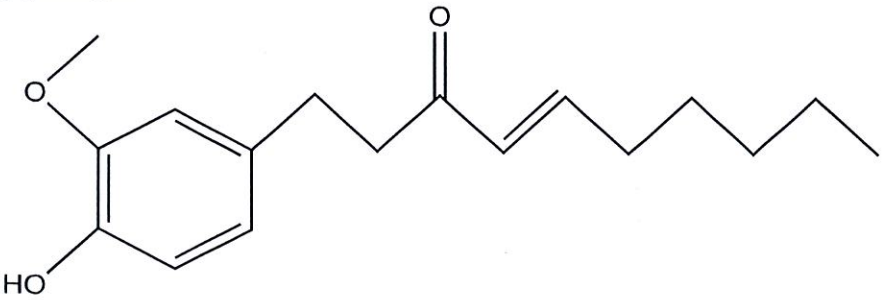
Species of Medicinal Ginger	Origin
Jamaican Ginger	Jamaica
Zingiber Officinale Roscoe	Western nations (USA)
Shokoyo (dried rhizome of Z. Officinale var. rubens)	Japan
Kankyo (steamed and dried rhizome of Z. officinale var rubens)	Japan
Red ginger (rhizome of Z. officinale var. rubra)	Indonesia
White ginger (rhizome of Z. officinale var amarum)	Indonesia

Ginger is a member of the plant family (Zingerbae) and can be found as many different species as shown in Table 2.[20-21] However, the species that has been studied is *Zingiber Officinale Roscoe*. Ginger has been shown to have at least 115 constituents in fresh and dried ginger. It is important to note that the individual components in ginger depend on origin, processor, and whether it is fresh, dried, or processed.[22] Methanolic extractions have been used to isolate 31 compounds in fresh ginger.[23] Of these isolated 31 compounds, 14 bioactive compounds have been found. These bioactive compounds are [4]-gingerol, [6]-gingerol, [8]-gingerol, [10]-gingerol, [6]-paradol, [14]-shogaol, [6]-shogaol, 1-dehydro-[10]-gingerdione, [10]-gingerdione, hexahydrocurcumin, tetrahydrocurcumin, gingerenone A, 1,7-bis-(4′ hydroxyl-3′ methoxyphenyl)-5-methoxyhepthan-3-one, and methoxy-[10]-gingerol.[24] However in regards to migraines the following bioactive compounds shown below have been noted to reduce inflammation and act as strong antioxidants.[25]

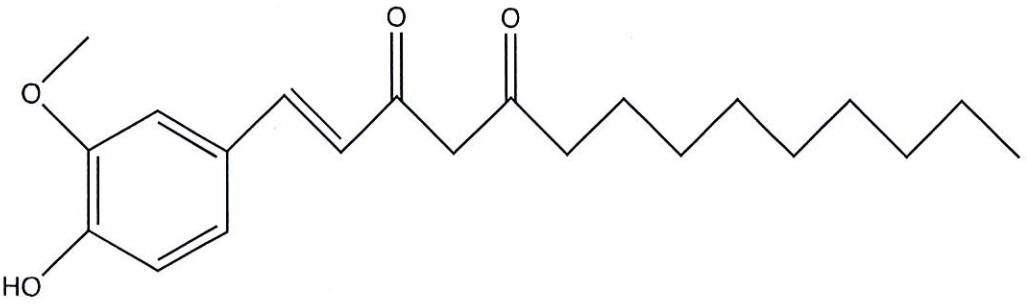
[6]-gingerol



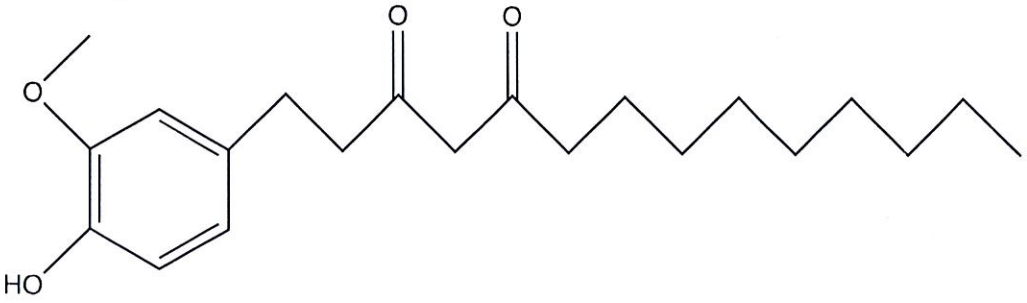
[6]-shogoal



1-dehydro-[10]-gingerdone



[10]-gingerdone



Relationship of Ginger & Migraines

It is believed that the Chinese and Indians have used Ginger for over 400 years in order to treat colds, arthritis, nausea, hypertension and migraines. Treatment of these ailments is due to the antioxidant, anti-inflammatory, anti-nausea, and anti-carcinogenic properties of ginger.[25] However in order to verify that ginger treats migraines a few studies have been done. For example, a study was done in order to compare the efficacy of ginger and sumatriptan (potent vasoconstrictor used to treat migraines) in a group of 100 men and women with acute migraine pain. The patients were given 250 mg of dried ginger powder or 50 mg sumatriptan. The participants recorded the time the headache began, headache severity before taking the capsule, and degree of pain relief afterward. The results showed that ginger was equally as effective sumatriptan in relieving headaches while demonstrating minor digestive symptoms.[26]

Another study that demonstrated the effectiveness of ginger in migraine was a double blind placebo control pilot study of sublingual feverfew and ginger. In this study, patients who have experienced migraine and met the international criteria for migraine were given sublingual feverfew/ginger capsule or a placebo. The results showed that 63% of patients receiving sublingual feverfew/ginger capsule found pain relief. This research showed that the sublingual ginger/feverfew is safe and should be used as the first line of defense for migraines.[27]

In addition to these studies, one study done by Ippoushi demonstrated a possible mechanism of action of ginger against migraines.[28] However, before looking into this mechanism, a brief explanation of immunology is needed in order to understand the experiment. In our primary line of defense, we have macrophages, which recognizes pathogens resulting in the recruit of other cells to the pathogen (inflammation) or destruction of the pathogen. Macrophages are able to do this because on the surface they have pathogen recognition receptors (PRRs) and recognize pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS). These macrophages will then bind to the pathogen and release radical oxygen such as nitric oxide in order to kill the pathogen.[29]

Using these ideas Ippoushi created a study in which he could stimulate the production of nitric oxide by injecting mice with LPS. In this study, Ippoushi found that in the LPS-stimulated mouse macrophage, [6]-gingerol inhibited NO production and reduced inducible nitric oxide synthase (iNOS), which is stimulated in response to stress.[28] Ippoushi work was later complemented by a researcher named Koh, who showed that [6]-shogoal, 1-dehydro-[10]-gingerdone, and [10]-gingerdone decreased LPS-induced NO production, and reduce iNOS expression.[30] Therefore the ability to inhibit the NO shows the vasoconstriction properties of ginger. In addition, this experiment is also supported by the structural properties of the bioactive

compounds shown above. The bioactive compounds of ginger are phenolic compounds, which can act as nitric oxide production inhibitors.[31]

Ginger has also shown the ability to partially activate 5-HT_{1A}, which induces vasoconstriction and reduces inflammation by inhibition of substance (CGRP, Substance P, NO) from trigeminal nerve causing redistribution of blood flow resulting in alleviation of migraine pain.[32] Based on this information we are able to draw conclusions that these bioactive compounds in ginger play a critical role in the inhibition of NO, which in turn play a role in the alleviation of migraines.

Hypothesis and Intent:

This information on migraines and ginger suggest structural similarities to vasoconstrictor drugs used to treat migraines. Therefore a structural analysis will be done in order to determine structural similarities between ginger and successful vasoconstrictor medications.

Due to limited resources, an experimental design will be created to focus on the receptor binding of vasoconstrictor drug and ginger in order to determine whether the binding interactions of these compounds are similar. The findings of these experiments may help to explain ginger's ability to alleviate migraine pain.

Conclusion:

A migraine is a brain disorder that can arise due to vasodilation. Vasodilation is caused by the activation of serotonin receptor leading to the release of NO (nitric oxide). The release of nitric oxide results in vasodilation and release of neurotransmitters such as calcitonin gene-related peptide and substance P resulting in pain. Ginger has the ability to alleviate migraine pain due to its ability to inhibit NO resulting in vasoconstriction. However, further research needs to be done in order to determine whether ginger has structural similarities to vasoconstrictor drugs. Additionally, an experimental design should be proposed in order to determine whether these compounds have similar binding interactions. These topics of migraine and ginger are both not completely understood, however, through further research the field of science could better comprehend these two topics.

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