Could glial activation be a factor in migraine?

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SUMMARY

Migraine represents a central neural hypersensitivity. During an attack, migraine sufferers can be hypersensitive to normal levels of sound, light, smell and movement. Sensory processing dysfunction in the brain stem or diencephalic nuclei has been implicated. Most scientific migraine research has focused on neuronal function because of their central role in the processing, integration and transmission of sensory information. However the supporting glia, their receptors and their secreted mediators are now recognised as having an important role in neuronal function regulation. Activated microglia and astrocytes produce and release a variety of neuroexcitatory substances including nitric oxide, excitatory amino acids and proinflammatory cytokines. Spinal glial activation and the subsequent release of proinflammatory mediators initiate and maintain a range of enhanced pain states. The focus on neuronal function has ignored the potential contribution of glial cell activation to neural hypersensitivity and pain. If the central neuronal hypersensitivity associated with migraine represents glial cell activation, drugs that block glial cell activation and the subsequent release of neuroexcitatory substances could have therapeutic potential in both acute migraine treatment and migraine prophylaxis.

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Background

In the 1960s, Melzack and Wall hypothesized incoming pain messages could be modified, either at the level of the spinal cord or by the brain. Their “gate theory” of pain replaced Cartesian “specificity theory”, which proposed injury activates specific pain receptors and fibres which, in turn, project pain through the spinal cord to a pain centre in the brain. Specificity theory taught the pain experience is proportional to the peripheral injury and the pathology. While this might be applicable in acute injury, this is not the situation in chronic pain.

The somatosensory nervous system operates over a continuum of pain processing states. In the normal state, there is appropriate processing of sensory input. In the suppressed state, there is reduced sensibility because of major activation of inhibitory systems in the dorsal horn. In the facilitated transmission state, there is increased excitability of the dorsal horn such that sensory thresholds are lowered. Central nervous system sensitization is characterized by increased (often exquisite) sensitivity to light touch, muscle tenderness, referred pain as well as local reddening and oedema. A large body of experimental and clinical evidence has shown that migraine, tension headache and sinus pain are manifestations of increased nervous system sensitization [1,2].

During a migraine attack sufferers can be hypersensitive to light, sound, smell and movement yet the intensity of the normal external cues remains the same. Allodynia (perception of pain with a normally non-painful stimulus) may be present during and sometimes after a migraine attack. Migraine probably results from a dysfunction of the brain stem or diencephalic nuclei involved in sensory processing [2]. Neural events in the brain stem result in ensuing dilation of blood vessels, which in turn results in pain and further neural activation. Brain imaging studies using positron-emission tomography show that the brain stem particularly the periaqueductal grey matter (PAG) is activated at the beginning of a migraine attacks [3]. The PAG is a major gateway to the limbic system and other sensory systems. Ergot and triptan receptors are present in the PAG. A variety of channelopathies have also been implicated in migraine, particularly familial hemiplegic migraine however our understanding in this area remains rudimentary [4].

The focus of most scientific migraine research has been the neurons and the transmission of neural signals because they are central to the processing, integration and transmission of information. This approach led to the development of the triptans - selective serotonin receptor agonists that activate $5HT_{1B/1D}$ receptors [4]. Similar research has seen the development of calcitonin gene related peptide (CGRP) inhibitors [5].

Traditionally the primary roles of the glia (astrocytes and microglia), the cells surrounding the neurons, have been perceived as involved with myelination and the maintenance of neuronal homeostasis. However the glia, their receptors and their secreted signalling factors also influence neural function [6]. The microglia and astrocytes when activated produce and release a variety of neuroexcitatory substances including reactive oxygen species, nitric oxide and inflammatory cytokines [7]. Spinal glial activation and the subsequent release of proinflammatory mediators has...
been implicated in the initiation and maintenance of a number of pain states [8]. Cyclooxygenase mechanisms have been implicated in the allodynia seen in migraine. This would also be in keeping with glial cell activation. Combined triptan/nonsteroidal anti-inflammatory drug (NSAID) combination therapies are more effective than either agent alone [9].

Toll like receptors (TLRs) are a range of receptors shared with bacteria and plants that recognize a diverse range of molecules (e.g. lipopolysaccharide [LPS] of gram-negative bacteria, heat shock proteins and cell membrane components released from damaged cells) that are also present on glia. TLR2 and TLR4 receptors in particular have been implicated in glial cell activation and subsequent neuroexcitation [8]. Opioid receptors are typically only blocked by the (−) - isomer of the opioid agonist naloxone. Naloxone blocks LPS TLR4 microglial activation, however both stereoisomers of naloxone exert identical inhibitory effects indicating that the glial receptors naloxone activates are not classical opioid receptors. A broader range of agonists and antagonists could potentially activate glial receptors. Both stereoisomers of naloxone are now known to antagonize TLR4 receptors. In the animal model when TLR4 glial receptors are blocked the animal returns to a normal basal pain state. Analgesia is not produced [8]. Other glial receptors and their agonists have yet to be elucidated.

Most of the research looking at glial activation in response to tissue trauma has focused on opioids. Morphine appears to act not only on the classical opioid receptors on neurons, but also on the glia receptors producing the same cascade of events that also results in increased hypersensitivity. At the same time that morphine is providing pain relief, the glial cells are also making neuroexcitatory mediators. The end additive result is a reduction in pain, however with increasing opioid doses glial activation increases leading to the phenomenon of analgesic tolerance. Opioid-induced glial activation can contribute to the allodynia and hyperalgesia that results from chronic opioid administration. The efficacy of morphine can be potentiated by targeting opioid-induced glial activation, or by neutralizing or antagonizing the action of proinflammatory cytokines. The enhanced analgesic effect of morphine secondary to chronic naloxone exposure was reported thirty years ago [10]. The phenomenon of both neuronal and glial activation is shared with other clinically relevant opioids [8].

Opioids are part of large family of naturally occurring substances called alkaloids. Morphine, caffeine, nicotine and ergotamine are all alkaloids. Morphine largely binds with the μ-opioid receptor. Caffeine binds to adenosine receptors while nicotine binds to nicotinic acetylcholine receptors. Ergotamine receptors are present in the periaqueductal gray matter. A number of alkaloids can influence the nervous system. The evidence would suggest that many food derivatives are able to pass into the systemic circulation and cross the blood brain barrier. Many modern drugs would simply not work if this were not possible. Despite a large body of scientific evidence the contributory role of foods to migraine [11,12] has remained largely ignored, because it is unable to be integrated with current neurological thinking. Many of the foods implicated in migraine and tension headache are alkaloids – particularly gluten [13,14]. Gluten, β caseinophrin and eggs, the commonest foods implicated in migraine are all recognized as having opioid like activity [15]. Other common foods linked to migraine such as citrus and tomato also have alkaloid properties. These foods potentially could activate opioid like receptors on the glial cells facilitating a central sensitization.

The Hypothesis

If the hypothesis that glial cell activation and the subsequent release of proinflammatory mediators initiate and/or maintain the neural hypersensitivity state seen in migraine then there are a number of “new” drugs that could potentially be used in migraine treatment. Drugs that block glial cell activation that could potentially be useful in the treatment of migraine include naltrexone [8], minocycline [16], pentoxifylline [16], propentofylline [17], AV411 (ibudilast) [18] and interleukin 10 [19]. Many of these drugs are already widely available, used for other indications and have been shown to have an excellent safety profile. Some of these drugs could be delivered using nasal delivery systems.

Evaluation of the hypothesis

The hypothesis can be simply evaluated by giving patients a drug such as naloxone intramuscularly or intravenously during an acute migraine attack or giving other drugs orally to prevent an attack.

Review of the literature shows that this hypothesis has already been partially evaluated. Naloxone has been trialled on a limited basis as a migraine treatment. When it was trialed the investigators were studying it from the perspective that migraine represented a failure of endogenous serotonergic and opioid production. The theory was that treatment with naloxone upregulated opioid receptors in the brain stem making them more available to the body’s natural endorphins. At that time these ideas were not in keeping with the incorrect medical paradigm of the time that migraine was a vasospastic disorder initiated by vasocnstriction in the cranial vasculature.

In the acute migraine situation, naloxone was shown to be effective in treating acute migraine attacks associated with scotoma but ineffective in treating acute common migraine attacks [20]. In two patients with non-familial hemiplegic migraine naloxone was shown to reverse the neurological deficits accompanying the attacks whereas the pain was unaffected [21]. In a clinical situation the author has successfully treated two chronic migraine patients with 400 micrograms of intramuscular naloxone.

In the migraine prophylaxis situation, fifty-four subjects who suffered from migraine refractory to other therapies were treated with intramuscular naloxone 150 mg/kg/day for three months. A 58% reduction in migraine attacks occurred. It took 2–3 weeks before patients noticed a difference and half of the patients also had a reduction in migraine frequency 3 months after treatment stopped [22]. Naltrexone, the oral equivalent of naloxone would appear to have significant promise in the prophylactic prevention of migraine.

A case of a migraine sufferer with medication overuse headache successfully treated with ibudilast has also been reported. Further study looking at the efficacy of ibudilast on migraine was suggested [23]. Vitamin D has also been reported as being a successful treatment in menstrual migraine [24]. While other mechanisms have been postulated, vitamin D also has a critical role in down regulating glial activation [25].

Consequences of the hypothesis

The focus of most scientific migraine research has been on drugs that influence the transmission of neural signals. Despite a large volume of research, apart from the development of the triptans, [4] this approach has been largely unproductive. A focus on glial cell activation would involve a paradigm shift in our understanding of migraine. A number of “new” drugs, some with an excellent clinical safety profile, would appear to offer considerable promise in both the acute and prophylactic treatment of migraine. Successful utilization of these drugs would also offer new perspectives on migraine pathophysiology.
References