Harnessing migraines for neural regeneration

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Abstract

The success of naturalistic or therapeutic neuroregeneration likely depends on an internal milieu that facilitates the survival, proliferation, migration, and differentiation of stem cells and their assimilation into neural networks. Migraine attacks are an integrated sequence of physiological processes that may protect the brain from oxidative stress by releasing growth factors, suppressing apoptosis, stimulating neurogenesis, encouraging mitochondrial biogenesis, reducing the production of oxidants, and upregulating antioxidant defenses. Thus, the migraine attack may constitute a physiologic environment conducive to stem cells. In this paper, key components of migraine are reviewed—neurogenic inflammation with release of calcitonin gene-related peptide (CGRP) and substance P, plasma protein extravasation, platelet activation, release of serotonin by platelets and likely by the dorsal raphe nucleus, activation of endothelial nitric oxide synthase (eNOS), production of brain-derived neurotrophic factor (BDNF) and, in migraine aura, cortical spreading depression—along with their potential neurorestorative aspects. The possibility is considered of using these components to facilitate successful stem cell transplantation. Potential methods for doing so are discussed, including chemical stimulation of the TRPA1 ion channel, conjoint activation of a subset of migraine components, invasive and noninvasive deep brain stimulation of the dorsal raphe nucleus, transcranial focused ultrasound, and stimulation of the Zusanli (ST36) acupuncture point.

Key Words: neuroprotection; neurorestoration; neurogenesis; stem cells; migraine; transient receptor potential ankyrin-1; calcitonin gene-related peptide; albumin; acupuncture; oxidative stress

Introduction

Since the discovery of neurogenesis in the adult mammalian brain, efforts have been made to use this capacity for purposes of neural regeneration. Approaches have included transplantation of exogenous or autologous stem cells, and the delivery of growth factors and other pharmaceuticals to stimulate innate neurogenesis (Carvalho et al., 2015).

However, there may already be an endogenous, integrated mechanism for increasing neural protection and repair that is physiologic and prevalent: the migraine attack. In this paper we will first review how the elements and feedback loops of a migraine attack may implement a neurorestorative function. We will then speculate on how migraine processes might be elicited to support exogenously administered stem cells in neural restoration.

Migraines and Oxidative Stress

Migraine attacks, prototypically lasting from 4 to 72 hours, involve moderate to severe throbbing pain that is increased by routine physical activity and accompanied by nausea and/or painful sensitivity to light and sound (Headache Classification Committee of the International Headache Society (IHS), 2013). In about 30% of cases, the migraine is preceded by visual aura, comprised of such experiences as scintillating lines and blind spots. During an attack, migraineurs feel and look ill.

In fact, these symptoms and the underlying physiology may defend the brain against oxidative stress (Borkum, 2018). Transient receptor potential ankyrin-1 (TRPA1) ion channels, found on pain-sensitive nerve endings in the dura mater, are able to detect oxidative stress and transduce it into a neural signal (Kozai et al., 2014). In turn, this signal elicits neurogenic inflammation, the cardinal feature of migraines, in animal models (Benemei et al., 2014).

In theory, the oxidative stress may have various sources, differing among migraineurs, including (1) mitochondrial defects (Welch et al., 1989; Markley, 2012) which tend to increase the production of superoxide (Stuart and Griffiths, 2012) and impair antioxidant defenses (Wu et al., 2014); (2) cortical hyperexcitability (Coppola et al., 2007), in which oxidative stress may result from the high metabolic rate of brain tissue; (3) excessive activity of vasoconstrictors such as angiotensin, which entails production of superoxide as a byproduct (Ripa et al., 2014); and (4) genetically less active antioxidant enzymes (Neri et al., 2015). Moreover, migraine triggers may be exposures that further raise levels of oxidants in the brain (Borkum, 2016).

Thus, oxidative stress may be a final common pathway, signaling any number of unfavorable conditions in the brain. Further, oxidative stress can itself be harmful, as the brain is uniquely exposed and susceptible to damage from oxidants. Such damage may be a key early step in neurodegenerative diseases (Cahill-Smith and Li, 2014).

Migraine attacks appear to be a naturalistic means for the brain to counteract this damage, by reducing the brain’s energy demands, strengthening antioxidant defenses, delivering a range of growth factors, boosting neurogenesis, preventing apoptosis, facilitating mitochondrial biogenesis, and supporting the survival, proliferation, development, and complex architecture of neurons. We will first review these aspects of migraine in detail, and then consider possible applications.

Elements of the Migraine Attack

The migraine attack unfolds as a complex, coordinated sequence of physiological processes (Goadsby, 2012), for which one starting point may be the stimulation of pain-sensitive nerve endings in the dura mater (Figure 1). This
stimulation may arise from a buildup of oxidative stress, as we have seen. Alternatively, in migraine with visual aura, a wave of activation is thought to propagate over the cortex, followed by a marked decrease in spontaneous firing (cortical spreading depression; CSD), corresponding to the aura’s scintillations and scotomas, respectively. The irritation of nociceptive nerve endings may then arise from the potassium ions and glutamate released by this activity, in addition to the oxidants it generates.

Irritation of nociceptive fibers causes them to release calcitonin gene-related peptide (CGRP) and substance P from their distal ends, instigating neurogenic inflammation. CGRP causes mast cell degranulation, vasodilation, hyperemia, and possibly further sensitization of nearby nociceptors. Substance P causes plasma protein extravasation into cerebrospinal fluid.

The activity of the pain fibers is transmitted proximally to the trigeminal nucleus caudalis and the thalamus, sensitizing central nociceptive pathways and contributing to the pain. The activation further spreads to such brainstem nuclei as the solitary tract nucleus (responsible for nausea and vomiting), the locus ceruleus and the hypothalamus (involved in the stress response), the basal ganglia (involved in pain modulation, neurogenic inflammation, and pain sensitization in the peripheral, and contributing to central sensitization in the trigeminal nucleus caudalis), and the dorsal raphe nucleus (DRN). The simultaneous firing of these regions is characteristic of a migraine attack.

Meanwhile, platelet activating factor (PAF) is released early in a migraine, causing platelets to aggregate in the cerebral venules. Platelets and presumably the DRN release serotonin which, via 5-HT_3 receptors in the blood vessels, activates endothelial nitric oxide synthase (eNOS) and raises production of nitric oxide. The platelets, in response to activation, and the endothelium, in response to nitric oxide, then release brain-derived neurotrophic factor (BDNF).

This stereotyped sequence of responses is further coordinated by feedback loops. Some are reinforcing and may sustain the migraine attack. Thus, serotonin, CGRP, substance P, PAF, and BDNF all raise the activity of eNOS. The resulting nitric oxide then facilitates the production of BDNF, and vice versa, in a positive feedback cycle (Monnier et al., 2017). Substance P and eNOS seem to be embedded in a similar cycle (Yonehara and Yoshimura, 1999, 2000).

There are also negative feedback loops that seem designed to prevent the neurogenic inflammation from triggering excessive classical inflammation. Thus, CGRP (Matsumoto et al., 1996) and nitric oxide (Golebiewska and Poole, 2015) limit platelet activation. Moreover, at least in the mouse peritoneal cavity, CGRP attenuates the movement of neutrophils and monocytes through the endothelium (Gomes et al., 2005) and thus CGRP may help to maintain the immune privilege of the CNS. Serotonin, directly through 5-HT_2C receptors (Hwang et al., 2008) and indirectly through the release of fractalkine (Cardona et al., 2006), limits the extent of microglial activation.

Migraines as a Healing Environment

Let us look more closely at these processes from the standpoint of neurorestoration.

Platelet activation

Platelets are classically thought to contribute to migraines by releasing serotonin, which may sensitize nociceptive nerve endings; proinflammatory cytokines, which may contribute to inflammation; and nitric oxide, adding to vasodilation (Danese et al., 2014).

However, activated platelets are also first responders to a site of injury, releasing a range of growth factors to support healing, including BDNF, platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), nerve growth factor (NGF), and transforming growth factor-β1 (TGF-β1) (Mancuso and Santagostino, 2017).

Not surprisingly, activated platelets in vitro facilitate angiogenesis, induce the survival and proliferation of neural stem cells, and support their differentiation into neurons and glia (Hayon et al., 2012a). In an in vivo model of cerebral ischemia, activated platelets help limit damage and facilitate repair of brain tissue (Hayon et al., 2012b).

Now, excessive platelet activation could cause a harmful procoagulant state. Moreover, platelets, by producing interleukin-1β and certain chemokines, create an inflammatory milieu, attracting monocytes and encouraging their differentiation into macrophages (Mancuso and Santagostino, 2017), potentially decreasing the viability of transplanted stem cells (Hermann et al., 2014). We have seen, however, that during a migraine attack, CGRP and nitric oxide serve to feed back and limit platelet activation.

Release of CGRP

CGRP is at the crux of migraines, causing mast cell degranulation, neurogenic inflammation, and pain sensitization in the periphery, and contributing to central sensitization in the trigeminal nucleus caudalis.

In addition, CGRP is protective, as it is a strong vasodilator, suppresses apoptosis of neurons under oxidizing (Schaeffer et al., 2003) and ischemic conditions (Abushik et al., 2017), reduces the expression of oxidant-generating NADPH oxidase (Zhou et al., 2010), and upregulates antiox-
idant enzymes (She et al., 2003).

CGRP also increases the expression of a number of neurotrophic factors, including glial cell line-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), NGF, VEGF, bFGF, and TGF-β (Russell et al., 2014; Ringer et al., 2017). Not surprisingly, then, CGRP increases neurogenesis in a mouse model of psychosocial stress (Hashikawa-Hobara et al., 2015).

In the brain, CGRP expression can be upregulated by injury and infection, and in turn can activate astrocytes and microglia (Reddington et al., 1995). This latter effect could work against the survival of transplanted stem cells. However, as noted, in migraine, serotonin, directly and via fractalkine, limits microglial activation.

CGRP has been used experimentally in stem cell grafting. In vitro, CGRP enhances survival and promotes the differentiation of adipose-derived stem cells into neurons (Yang et al., 2014). In an in vivo model of spinal cord injury, CGRP had a chemotactic effect, attracting intrathecally injected human umbilical cord stem cells to the site of injury, at least in transection lesions (Zhang et al., 2016). Clinically, CGRP has been explored for preventing vasospasm following surgery for subarachnoid hemorrhage (European CGRP in Subarachnoid Haemorrhage Study Group, 1992).

**Substance P**

Substance P mediates the extravasation of plasma proteins, chiefly albumin, into cerebrospinal fluid. Albumin is protective as it is an antioxidant (Tafera et al., 2013), carries unsaturated fatty acids that may aid in the repair of neuronal membranes (Rodriguez de Turco et al., 2002), and stimulates astrocytes to produce oleic acid, which facilitates the differentiation of neurons (Bento-Abreu et al., 2008).

In mice, IV injection of substance P markedly increases neural stem cell proliferation and differentiation into neurons, and leads to anatomical recovery after spinal cord injury. Substance P also promotes functional recovery, suggesting successful integration of the newly formed cells into neural networks (Yang et al., 2017). In ischemia, protein leakage through the blood-brain barrier seems to induce neurogenesis in latent niches throughout the midline circumventricular system (Lin et al., 2015).

**Activation of eNOS**

Nitric oxide, produced by eNOS that has been activated by serotonin, contributes to the vasodilation of migraines and to the release of substance P. Nitric oxide also protects the brain under ischemic conditions through a number of mechanisms including vasodilation, antioxidant action of production by the renin-angiotensin system (González et al., 2014), induction of antioxidant enzymes (Astort et al., 2014), and stimulation of mitochondrial biogenesis (Nisol et al., 2005). Moreover, activated eNOS causes the endothelium to release VEGF and BDNF (Zhang et al., 2003; Monnier et al., 2017).

The endothelium is an important component of stem cells’ neurovascular niche. Thus, eNOS can induce the proliferation, differentiation, and migration of neural progenitor cells (Chen et al., 2005) and spur angiogenesis (Asada et al., 2009). A nitric oxide donor increased neurogenesis and functional recovery in a rat model of ischemic stroke (Zhang et al., 2001).

**BDNF**

Production of BDNF by neurons and the endothelium is increased in migraine, and it released as well by activated platelets. It is thought to promote central pain sensitization in migraine attacks.

In addition, through uncoupling protein 2, BDNF decreases the production of oxidants by the mitochondria, and BDNF upregulates a number of antioxidant enzymes and proteins (Wu et al., 2016). In addition, of course, BDNF is a growth factor, and seems to underlie endogenous neuroprotection (Larsson et al., 1999), angiogenesis (Bowling et al., 2016) and the increased neurogenesis from exercise and antidepressant treatment (Vilar and Mira, 2016). BDNF has been used in mice models of traumatic brain injury (TBI) (Kim et al., 2016) and spinal cord injury (Robinson and Lu, 2017) to support the survival of neural stem cells, their differentiation into neurons, and possible integration into neural circuits.

**Serotonin**

Serotonin is released by platelets at the start of a migraine (Ferrari et al., 1989). Moreover, there is increased firing in the region of the dorsal raphe nucleus (Weiller et al., 1995), which may distribute serotonin throughout the cortex (Azmitia, 2007). These seem to reverse a serotonin deficit that intensifies in the days leading up to a migraine (Hamel, 2007). Serotonin is thought to participate in an attack by promoting inflammation and sensitizing pain receptors.

In addition, serotonin has antioxidant properties in vitro (Kalogiannis et al., 2016). In vivo it causes astrocytes to release metallothioneins, a class of antioxidant enzyme, and cysteine, which is taken up by neurons and used to produce the antioxidant glutathione (Miyazaki and Asanuma, 2016). Serotonin is also a growth factor and induces the release of such other trophic factors as BDNF, VEGF (Greene et al., 2009), IGF-1 (Aberg et al., 2003), and S100B (Miyazaki and Asanuma, 2016). Through BDNF, serotonin increases the proliferation and migration of neural stem cells in the subventricular zone (Chiararolli et al., 2007).

Note that if release of serotonin were the only component of migraine, it could work against tissue healing by promoting vasoconstriction. However, this property of serotonin is antagonized in migraine by nitric oxide and CGRP.

Serotonin agonists have been used in animal models of TBI (Cheng et al., 2016) and a clinical trial following ischemic stroke (Chollet et al., 2011) to promote recovery.

**Cortical spreading depression (CSD)**

CSD is thought to underlie migraine aura (Lauritzen, 1994). In CSD, a wave of activation and reactive hyperemia spreads geographically over the cortex, leaving in its wake a region of diminished cortical firing. These are believed to correspond, respectively, to the scintillations and scotomas of aura. Acutely, CSD raises oxidant production (Shatillo et al., 2013). This is followed by a number of processes that protect against subsequent ischemia, including activation of AMP kinase and downregulation of energy-demanding pathways (Viggiano et al., 2014), increased transcription of antioxidant enzymes and proteins (Choudhuri et al., 2002), and induction of uncoupling protein 2, which reduces production of superoxide by the mitochondria (Viggiano et al., 2016).
Further, the intense neuronal activation and consequent increased blood flow in CSD markedly upregulates the production of BDNF and transcription of the gene for its receptor, TrkB (Urbach et al., 2006). In this sense, CSD resembles electrical stimulation protocols to improve functional recovery after stroke or brain injury (Henrich-Noack et al., 2017).

Thus, migraine attacks appear to be an integrated set of homeostatic processes that defend the brain against oxidative stress. Moreover, each component of migraine seems to facilitate the survival, proliferation, differentiation, and/or migration of stem cells. These effects are summarized in the Table 1.

Prospects for Harnessing Migraines
For both grafted and endogenous stem cells, efficacy depends on a facilitative environment in the injured tissue (Hermann et al., 2014). Moreover, it is unlikely that any single molecule will be sufficient for neural regeneration; rather, combination strategies are needed (Hermann and Chopp, 2012; Morales et al., 2016). As we have seen, migraine attacks seem to function in a multifaceted way to provide a healing milieu.

For successful neural repair, stem cells must proliferate, differentiate, migrate, mature, survive, and become integrated into existing neural circuits (Jones and Connor, 2017). These processes, in turn, are affected by chemicals secreted in the microenvironments of the neurogenic niches and the target injured brain region, particularly neurotrophic factors (Carvalho et al., 2015).

However, the administration of these growth factors is hampered by their short half-lives in the body, rapid degradation, and poor ability to cross the blood–brain barrier (Carvalho et al., 2015). Moreover, an oversupply of neurotrophins is associated with epilepsy, autism and bipolar disorder, suggesting that their concentration in the brain must be tightly regulated (Carvalho et al., 2015). Stem cells themselves carry the theoretical risk of creating benign (Amariglio et al., 2009) or malignant tumors (Hermann et al., 2014).

Technologies are being developed to circumvent these problems, such as encapsulating neurotrophins in nanoparticles structured to protect the drug, provide sustained release, and target specific brain regions through receptor binding (Angelova et al., 2013; Angelov and Angelova, 2017; Angelova and Angelov, 2017; Guerzoni et al., 2017). However, the body may have its own techniques for enhancing the availability of growth factors. In particular, a migraine attack, by creating a physiologic environment conducive to neural repair, might be a naturalistic way of upregulating neurotrophic signaling, and provide a fertile ground for the successful utilization of stem cells.

This raises the question – admittedly speculative – of purposefully drawing on migraine physiology in stem cell treatments. At this point, little is known to guide such a project. Logically, however, three broad approaches could be taken: (1) eliciting a full migraine attack combined with pain suppression; (2) eliciting a subset of migraine components; and (3) eliciting a subthreshold analogue of migraines.

Full migraine
An obvious way of eliciting a migraine, of course, would be to stimulate TRPA1 ion channels chemically. A range of naturally occurring molecules including thymol, ethyl vanillin, allyl isothiocyanate, cinnamaldehyde, and hydrogen sulfide open TRPA1 ion channels (Wu et al., 2017a; Weinhold et al., 2017). At least in skeletal muscle, TRPA1 agonists seem to activate stem cells (satellite cells) and facilitate their migration and early differentiation into myoblasts (Osterholz et al., 2016).

However, the effect of such an intervention may depend on the specific disorder. Thus, in a transgenic mouse model of Alzheimer’s disease, TRPA1 ion channels are more numerous on cortical neurons and hippocampal astrocytes than in wild type mice. Moreover, stimulation of this channel led to increased production of proinflammatory cytokines, increased deposition of amyloid beta, and exacerbation of behavioral deficits (Lee et al., 2016), suggesting that at least in genetic Alzheimer’s disease there may be a specific vulnerability to TRPA1 agonists. TRPA1 also contributed to cell death in a retinal model of ischemia (Araújo et al., 2017) but protected cardiac myocytes during reperfusion (Lu et al., 2016). Thus, the safety and efficacy of TRPA1 agonists would need to be assessed carefully in a context-dependent manner.

Subsets of migraine components
Several techniques that we can now understand to be eliciting parts of a migraine attack have already been studied. One such approach draws on Raskin et al.’s (1987) observation that deep brain stimulation (DBS) of the DRN can elicit a migraine-like headache. The DRN is one of the brainstem nuclei whose coordinated firing characterizes a migraine attack. DBS of the raphe nuclei improved working memory in an animal model of TBI (Carballosa Gonzalez et al., 2013).

Of course, DBS carries the risks of an invasive procedure. Moreover, Raskin et al. (1987) describe individuals for whom the migraine-like headaches were continuous and intractable. However, recent techniques may allow more moderate and noninvasive stimulation. Thus, oscillating high frequency electric fields can be positioned to interfere at a frequency that will influence neural firing at the desired depth in the brain (Grossman et al., 2017).

There may be other ways of eliciting aspects of the migraine attack by physical means. Thus, transcranial focused ultrasound with microbubbles has been used to transiently open the blood–brain barrier for delivery of drugs and to promote neurogenesis (Scarcelli, et al., 2014). This leads to sterile inflammation that shares certain features with migraine, including extravasation of albumin and other plasma proteins, and upregulation of VEGF and BDNF (Kovacs et al., 2017). However, the sterile inflammation has also included activation of microglia, increased proinflammatory cytokines, and migration of macrophages to the affected area, suggesting classical inflammation, which can result from protein extravasation (Ralay Ranaivo and Wainwright, 2010). This may reflect overly intense treatment parameters (McMahon and Hynynen, 2017), with research needed to ascertain whether with gentler stimulation the effects can be restricted to neurogenic inflammation.

A milder and more physiologic approach would be to simulate several features of a migraine attack simultaneously. The cholinesterase inhibitor donepezil improves spatial learning in mice by causing hippocampal astrocytes to release CGRP (Narimatsu et al., 2009) and presumably downstream growth factors. We have seen that serotonin agonists, BDNF, CGRP, substance P, and a nitric oxide donor have...
been studied individually for promoting stem cell grafting and/or functional recovery. Considering migraine as an integrated system, conjoint activation of these processes might be more effective (Table 1).

Subthreshold analogue of migraine
An alternative to activating parts of a migraine attack would be to elicit a subsyndromal version of an attack. Whether this is feasible is not yet known. Interestingly, however, there is evidence that stimulation of the Zusanli (ST36) acupuncture point, just below the anterolateral knee, increases serotonin content of the DRN (Wu et al., 2017b), raises serotonin levels of BDNF (Tao et al., 2014), stimulates hippocampal neurogenesis after ischemia (Tao et al., 2014), suppresses apoptosis (Chavez et al., 2017), and may raise levels of activated eNOS (Leung et al., 2016), CGRP (Lee et al., 2012) and brain antioxidant defenses (Chavez et al., 2017). Thus, stimulation of this acupuncture point appears to replicate many of the neuroprotective features of migraine without the pain of a full attack.

Pain suppression
Of course were a full migraine attack to be elicited, it would need to be dissociated from pain in order to be of clinical value. Presumably this can be facilitated with analgesic medications that do not limit neurogenic inflammation. Alternatively, it might theoretically be possible to create a “pain-free migraine” by simultaneous use of TRESK potassium channel agonists. The TRESK channel, expressed primarily in neurons of the trigeminal, dorsal root, and autonomic ganglia, appears to decrease neuronal excitability in response to exposure to histamine, and thus may reduce pain under inflammatory conditions (Lafrenière and Rouleau, 2011). A very small number of individuals, all of them having migraine with typical visual aura, have been found to have a frameshift mutation in which TRESK channels are non-functional (Lafrenière and Rouleau, 2011). In theory, then, a TRESK agonist might make it possible to bring about a migraine attack without inducing pain.

At this point, it is unknown whether such a “migraine” is possible or would have neurorestorative properties. However, we have seen that individual migraine components indeed assist in neural repair, suggesting that pain is not an obligatory feature for migraines to be of use.

Conclusions
Thus, the idea that migraine attacks are an endogenous, integrated mechanism for neural repair, suggests their possible use in creating a healing environment for application in stem cell technology. Nonetheless, this possibility is still in its infancy. Research to find effective chemical or mechanical techniques for eliciting components of a migraine, dissociating these components from pain, and studies to determine safety and dosing in various pathophysiological contexts will be key. Stimulation of the Zusanli (ST36) acupuncture point seems a particularly promising candidate.

5-HT: Serotonin; BDNF: brain-derived neurotrophic factor; CGRP: calcitonin gene-related peptide; CSD: cortical spreading depression; eNOS: endothelial nitric oxide synthase.

| Neuroprotective properties | Platelet activation | Release of CGRP | Release of substance P/plasma protein extravasation | Activation of eNOS | Release of BDNF | Release of 5-HT | CSD |
|----------------------------|---------------------|-----------------|--------------------------------------------------|------------------|----------------|----------------|-----|
| ↓ Production of oxidants   | ↑                   | ↑               | ↑                                                | ↑                | ↑              | ↑              | ↓   |
| ↑ Antioxidant defenses     | ↑                   | ↑               | ↑                                                | ↑                | ↑              | ↑              | ↓   |
| Vasodilation               | ↑                   | ↑               | ↑                                                | ↑                | ↑              | ↑              | ↓   |
| ↓ Energy demands           | ↑                   | ↑               | ↑                                                | ↑                | ↑              | ↑              | ↓   |
| ↑ Mitochondrial biogenesis | ↑                   | ↑               | ↑                                                | ↑                | ↑              | ↑              | ↓   |
| Release neurotrophic factors | ↑               | ↑               | ↑                                                | ↑                | ↑              | ↑              | ↓   |
| ↓ Apoptosis of Neurons     | ↑                   | ↑               | ↑                                                | ↑                | ↑              | ↑              | ↓   |
| ↑ Angiogenesis             | ↑                   | ↑               | ↑                                                | ↑                | ↑              | ↑              | ↓   |
| ↑ Neurogenesis             | ↑                   | ↑               | ↑                                                | ↑                | ↑              | ↑              | ↓   |
| Already tested experimentally | ↑               | ↑               | ↑                                                | ↑                | ↑              | ↑              | ↓   |

Table 1 Migraine components

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