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Views and Perspectives

The Migraine Attack as a Homeostatic, Neuroprotective Response to Brain Oxidative Stress: Preliminary Evidence for a Theory

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Background.—Previous research has suggested that migraineurs show higher levels of oxidative stress (lipid peroxides) between migraine attacks and that migraine triggers may further increase brain oxidative stress. Oxidative stress is transduced into a neural signal by the TRPA1 ion channel on meningeal pain receptors, eliciting neurogenic inflammation, a key event in migraine. Thus, migraines may be a response to brain oxidative stress.

Results.—In this article, a number of migraine components are considered: cortical spreading depression, platelet activation, plasma protein extravasation, endothelial nitric oxide synthesis, and the release of serotonin, substance P, calcitonin gene-related peptide, and brain-derived neurotrophic factor. Evidence is presented from in vitro research and animal and human studies of ischemia suggesting that each component has neuroprotective functions, decreasing oxidant production, upregulating antioxidant enzymes, stimulating neurogenesis, preventing apoptosis, facilitating mitochondrial biogenesis, and/or releasing growth factors in the brain. Feedback loops between these components are described. Limitations and challenges to the model are discussed.

Conclusions.—The theory is presented that migraines are an integrated defensive, neuroprotective response to brain oxidative stress.

Key words: migraine, oxidative stress, growth factor, neuroprotective, homeostasis, regenerative

Abbreviations: AMPK adenosine monophosphate-activated protein kinase, BACE1 β-site amyloid precursor protein cleaving enzyme 1, BDNF brain-derived neurotrophic factor, bFGF basic fibroblast growth factor, CGRP calcitonin gene-related peptide, CREB cyclic AMP-response element-binding transcription factor, CSD cortical spreading depression, DRN dorsal raphe nucleus, eNOS endothelial nitric oxide synthase, ERK extracellular signal regulated kinase, FGF fibroblast growth factor, GDNF glial cell line-derived neurotrophic factor, IGF-1 insulin-like growth factor-1, iNOS inducible nitric oxide synthase, MAPK mitogen activated protein kinase, NADPH nicotinamide adenine dinucleotide phosphate, NF-κB nuclear factor-kappaB, NGF nerve growth factor, Nrf2 nuclear factor (erythroid-derived 2)-like 2, PAF platelet activating factor, PDGF platelet-derived growth factor, PI3K phosphoinositide 3-kinase, PKC protein kinase C, PLC-γ1 phospholipase C-gamma1, PPE plasma protein extravasation, pTrkB phosphorylated tropomyosin-related kinase B, SSRI selective serotonin reuptake inhibitor, TGF-β1 transforming growth factor-beta1, tPA tissue plasminogen activator, TrkB tropomyosin-related kinase B, TRPA1 transient receptor potential ankyrin-1, VEGF vascular endothelial growth factor

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Migraines are a multifaceted neurological disorder comprised of head pain, nausea or vomiting, and/or painful avoidance of light and sound, and aggravated by or causing avoidance of routine physical activity.[1] Five lifetime attacks are required for diagnosis (two for migraine with aura) because isolated migraine attacks can affect nearly anyone, and resemble secondary headaches due to such threats to the brain as meningitis and carbon monoxide poisoning.

Current understandings of migraine focus on cortical hyperexcitability,[2,3] activation of the trigeminovascular system,[4] and dysregulation of brainstem regions involved in antinociception and vascular control.[5-7] However, there is also an additional, minor paradigm: that migraine attacks are an adaptive, compensatory reaction. Thus, Loder observed that their partial heritability and high prevalence make it likely that migraines confer an evolutionary advantage, such as a defense against threats to the nervous system.[8] Goadsby suggested that the vasodilation of migraines is a "neural protection system" against excessive vasoconstriction.[9] And Cortelli and Montagna noted that the visceral pain of migraine and the immobility, sleep, and aversion to sensory stimulation that it incites seem well positioned to ameliorate a brain energy imbalance.[10]

In this article, we will propose and consider the merits of a particular adaptive theory of migraine attacks: that they are an integrated defensive response to oxidative threats to the brain. The goal is to provide a starting point for discussion.

MIGRAINES AND OXIDATIVE STRESS

Vulnerability to migraines is not completely understood but may be in part related to higher levels of lipid peroxides found in plasma, platelets, and urine of migraineurs between attacks.[11-13] Lipid peroxides are oxidation products and thus a biomarker of oxidative stress.[14] The reason for higher levels interictally in migraineurs is unclear but may reflect lower activity of certain antioxidant enzymes,[13,15] and/or increased activity of oxidant-generating vasoconstrictors such as angiotensin,[16,17] endothelin-1,[18] or urotensin-2.[19] Alternatively, the source may be cortical hyperexcitablity,[2] perhaps resulting in excessive oxidant production as a byproduct of the high metabolic rate.[20] Moreover, migraines may be associated with mitochondrial defects,[21-25] which tend to increase production of oxidants[26] and downregulate antioxidant enzymes.[27] Of course, more than one of these processes may be involved; oxidative stress may be a final common pathway for a number of unfavorable conditions in the brain.

Lipid peroxides are plausible signaling molecules for oxidative stress because they have long half-lives, and no net charge, and thus are able to diffuse, reaching receptors.[14] In fact, there appear to be dedicated receptors for oxidative stress on nociceptive nerve endings in the perivascular meninges.[28] Specifically, TRPA1 ion channels (transient receptor potential ankyrin type 1) open when certain of its cysteine residues are oxidized, admitting calcium ions and transducing the oxidizing conditions into a neural signal.[29] Moreover, in animal models, activation of the TRPA1 ion channel is sufficient to trigger neurogenic inflammation, a key component of migraines.[30]

Migraine triggers may be exposures that further increase oxidative stress.[20,31] For certain putative triggers, hydrogen peroxide is a byproduct of detoxification, for example when tyramine is metabolized by monoamine oxidase or when alcohol is processed by cytochrome P450-2E1. Other triggers appear to cause oxidant production by the microglia, neurons, and astrocytes as part of host defense. These triggers include infection, air pollution (particulate matter), aspartame, hypoxia, hypoglycemia and, potently, psychosocial stress,[32] which in the natural world may connote a high probability of imminent attack and infection. Other triggers may raise oxidant production by increasing the rate of oxidative phosphorylation, potentially extending to excitotoxicity. These may include, in susceptible individuals, monosodium glutamate, aspartame (via its aspartic acid moiety), hypoglycemia, and perhaps exposure to noise and mental overwork. For still other triggers, the oxidant production may arise from mitochondrial dysfunction. Alcohol, formate (a metabolite of aspartame),

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and β-phenylethylamine (found in chocolate) fall in this category.[20]

Thus, migraineurs may have a higher level of oxidative stress between attacks and migraine triggers may increase oxidant production further. The TRPA1 ion channel may provide a mechanistic link to migraines, eliciting neurogenic inflammation in response to oxidative stress.

Being able to detect and respond to oxidative stress would be adaptive, as the brain's polyunsaturated (easily oxidized) neuronal membranes, the presence of transition metal ions that can catalyze free radical reactions, high metabolic rate, and relatively weak antioxidant defenses make it uniquely exposed and susceptible to damage from oxidants.[33] In turn, this damage may be an early step in neurodegenerative diseases such as Alzheimer's or Parkinson's.[34]

However, if migraines are plausibly a response to brain oxidative stress, what type of response are they? In this article, we will explore the possibility that they are a coordinated set of mechanisms that deliver antioxidants and growth factors to the brain, reverse oxidative stress, prevent apoptosis, and support the survival, proliferation, development, and complex architecture of neurons. Indeed, there is evidence that numerous components of migraine physiology may be designed to protect and repair the brain.

Components of Migraine.—Before considering this theory, let us first review the main components of a migraine attack, drawing on current understanding of migraine pathophysiology. The concern here is not for the precise order or timing of the components, but simply a delineation of the components themselves.

Episodic migraine is classically thought to be a functional neurovascular disorder of the brain.[35] Initially, in migraine aura a wave of depolarization and hyperemia, followed by oligemia and suppression of spontaneous neural activity, propagates geographically over the cortex, producing such aura symptoms as scintillations and scotomas (cortical spreading depression; CSD). In migraine without aura, the situation is less clear but may involve "silent" CSD in nonsensory, nonmotor regions of the cortex. The high concentration of glutamate and potassium ions from CSD is thought to irritate the small diameter nociceptive fibers surrounding the cerebral blood vessels, venous sinuses, and dura mater. (As we have seen, it is likely that nociception can be initiated also by the products of reactive oxygen and nitrogen species.) This causes the fibers to release substance P and calcitonin gene-related peptide (CGRP),[36] initiating neurogenic inflammation of the dura mater, with mast cell degranulation, vasodilation, hyperemia, plasma protein extravasation (PPE) from the postcapillary venules, platelet aggregation in the venules, and possibly further sensitization of the nociceptors.[37] Activation is conveyed by these nociceptive fibers to the trigeminal nucleus caudalis and the thalamus, where sensitization of second and third order neurons, perhaps in part through CGRP,[38] contributes to the pain of migraine.

The trigeminal nucleus also conveys the nociceptive signal to a range of nuclei in the brainstem, hypothalamus, and basal ganglia,[39] likely including the dorsal raphe nucleus (DRN). Platelets and presumably the DRN release serotonin that, via 5-HT_{2B} receptors in the blood vessels, activate endothelial nitric oxide synthase (eNOS), increasing the production of nitric oxide. In turn, eNOS[40] and platelet activation[41] likely cause release of brain-derived neurotrophic factor (BDNF) from the endothelium and platelets, respectively.

Aspects of Neuroprotection.—There are signaling pathways within neurons that protect them against apoptosis in oxidizing conditions, suppress the production of oxidants and facilitate their detoxification, support the development of synapses and the elaborate arborization of dendrites, repair neurons after injury, and facilitate neurogenesis—the birth of new neurons.

The most important of these pathways are:[42-44]

- A pathway from phosphoinositide 3-kinase (PI3K) to Akt (protein kinase B), which suppresses certain transcription factors (p53, forkhead FKHRL1) and facilitates others (nuclear factor-kappaB/NF-κB)
- A pathway through extracellular signal regulated kinases (ERK), a type of mitogen-activated protein kinase (MAPK), which ultimately activates

the cyclic AMP-response element binding transcription factor (CREB), and
- A pathway through phospholipase C-γ1 (PLC-γ1), which activates a number of enzymes including protein kinase C (PKC).

These signaling cascades are set in motion by various neurotrophic factors such as BDNF, nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and basic fibroblast growth factor (bFGF or FGF2).[43] In particular, BDNF can activate all three signaling pathways.[43,44]

Thus, given that migraines may be a response to increased levels of oxidative stress in the brain, in what follows we will explore whether any of the components of migraine can deliver antioxidants to the brain, decrease the production of oxidants, and/or activate the signaling pathways of neural protection and repair. In doing so, we will draw on in vitro data and on animal and, where available, clinical, studies of ischemia. The appropriateness of using ischemia as a model condition will be discussed at the end of this article.

COMPONENTS OF MIGRAINE THROUGH THE LENS OF NEUROPROTECTION

Platelet Activation.—Migraines involve platelet activation and aggregation.[45-47] In particular, levels of the highly potent platelet activating factor (PAF) rise in the internal jugular venous blood during spontaneous migraine attacks.[48] In turn, platelets release serotonin, which may sensitize nociceptive fibers around pial and intracerebral blood vessels; proinflammatory cytokines, contributing to neurogenic inflammation; and nitric oxide, which is vasodilatory.[45]

Classically, of course, platelets are responsible for hemostasis. However, once activated, platelets also deliver a range of growth factors that promote tissue healing and regeneration. These include vascular endothelial growth factor (VEGF), FGF, platelet-derived growth factor (PDGF), transforming growth factor-β1 (TGF-β1), NGF, and BDNF.[41,49] These molecules, in turn, switch on (phosphorylate) growth-oriented cell signaling cascades such as the ERK and Akt pathways. By these means, platelets create a healing environment at a site of injury.[50]

This appears to be true in the brain as well. Acting in part through VEGF, FGF, and PDGF by shedding microparticles, activated platelets induce neural stem cell survival, proliferation, and differentiation into neurons and glia, as well as stimulating angiogenesis, in vitro,[50] and are neuroprotective and neuroregenerative in an in vivo model of cerebral ischemia.[51] This has led to the theory that platelets participate in the housekeeping of nervous tissue.[52]

Plasma Protein Extravasation.—In extravasation, proteins from blood serum leak into cerebrospinal fluid. The function of PPE in migraine is unclear. However, substance P, which elicits PPE, protects neurons from apoptosis in vitro.[53] Further, the most abundant serum protein is albumin, which is an antioxidant. In serum, 70% of the capacity to neutralize free radicals is from albumin specifically.[54] Logically, after extravasation into cerebrospinal fluid during migraine, albumin may play an antioxidant role in the brain.

In animal models of ischemic stroke, intravenous administration of human albumin leads to its extravasation and uptake by cerebral neurons. These neurons, in turn, seem to be protected from damage[55,56] and cortical infarct volume is reduced.[57] Albumin, which carries polyunsaturated fatty acids, seems to help in the repair of neuronal cell membranes.[58] Further, albumin administered in vitro to astrocytes is taken up by the megalin receptor and causes the production of oleic acid, which is neurotrophic, facilitating the differentiation of neurons.[55,59,60]

Unfortunately, in a large clinical trial of ischemic stroke, high dose IV albumin did not improve outcome,[61] apparently because adverse events balanced out the treatment effect.[62] Preliminary clinical trial data, however, suggest that IV albumin may help prevent delayed cerebral ischemia and cerebral infarction following subarachnoid hemorrhage.[63]

Production of Nitric Oxide.—An early event in migraine is activation of eNOS or NOS-3,[64] likely through the 5-HT_{2B} receptor.[65] The nitric oxide so produced contributes to the vasodilation in migraines and, by stimulating the release of substance P, to extravasation.[66]

In addition, in the vasculature, nitric oxide downregulates the renin-angiotensin system by inhibiting the production of angiotensin-converting enzyme and angiotensin-II AT_1 receptors.[67] Angiotensin increases oxidant production by strongly activating the enzyme nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase)[67] and thus its downregulation by nitric oxide has an antioxidant effect.

Moreover, eNOS is thought to protect against neuronal damage under hypoxic or ischemic conditions.[68] In part, this is by helping to maintain cerebral blood flow[69] and in part, nitric oxide, acting through cyclic GMP and the Nrf2 (nuclear factor [erythroid-derived 2]-like 2) transcription factor, induces antioxidant enzymes and proteins including heme oxygenase-1 and sestrin2.[70-72] Endothelial nitric oxide facilitates mitochondrial biogenesis and the production of ATP,[73] potentially correcting for mitochondrial dysfunction[22] and impaired brain energetics[23-25] as diatheses for migraine. And endothelial nitric oxide can also induce angiogenesis,[74] and the proliferation and migration of neural progenitor cells,[75] components of tissue repair.

Endothelium-derived nitric oxide contributes to synaptic plasticity and long-term potentiation in the brain,[76] in part because the blood vessel endothelium, in the presence of active (phosphorylated) eNOS, releases BDNF into the brain.[40] Indeed, the blood vessel endothelium is a major source of cerebral BDNF,[77] with endothelial cells producing BDNF at 50 times the rate of neurons.[78] In turn, BDNF may enhance vasodilation and the release of nitric oxide in a positive feedback loop.[77,79] Thus, the paradigm that migraines are an integrated neurovascular phenomenon[4] extends to neural protection and repair.

Brain-Derived Neurotrophic Factor.—BDNF is the most abundant and most studied of the trophic factors in the brain.[80] Serum levels of BDNF seem to rise during attacks.[81] Moreover, platelet levels are lower in migraineurs,[82] suggesting that the platelets release BDNF as part of their activation during the migraine process.[83] Expression of the gene encoding BDNF increases 15-fold 3 hours after CSD in the rat, while expression of the gene for its receptor triples.[84] In vitro, BDNF is released from trigeminal ganglion neurons in response to stimulation by CGRP.[85]

BDNF plays a key role in central sensitization[86] including, potentially, in migraine. However, it also appears to have a larger, neuroprotective role. Acting through the tropomyosin-related kinase B (TrkB) receptor, BDNF seems to preserve neural progenitor cells, prevent the degeneration of cortical neurons,[87,88] promote the formation, maintenance, and plasticity of synapses,[88] and support the consolidation of memory from short-term to long-term stores.[87]

At least in rats, BDNF is also involved in neural repair, promoting recovery from spinal cord injury and, in the brain, rescuing synapses and cognition after experimental transient ischemia[89-92] and psychosocial stress.[93] TrkB is found in blood vessels and its stimulation promotes angiogenesis,[87] particularly relevant after ischemia. Neurogenesis from exercise, an enriched environment, or chronic treatment with antidepressants seems to depend on increased BDNF.[94]

Moreover, BDNF signaling sets in motion an array of antioxidant processes, including upregulation of the enzymes glutathione reductase and superoxide dismutases; sulfiredoxin, an antioxidant protein that protects mitochondria; and sestrin2, a protein that regenerates oxidized peroxyredoxins and upregulates the Nrf2 antioxidant transcription factor.[95,96] By means of mitochondrial uncoupling protein 2, BDNF also decreases the production of superoxide, a free radical, by limiting the leakage of electrons from the electron transport chain.[96]

Thus, BDNF plays a large role in brain protection and repair. Not surprisingly, then, increasing BDNF levels has been proposed as a treatment strategy for Parkinson's disease,[97] Huntington's chorea,[98] and stroke rehabilitation.[99]

CGRP Release.—CGRP is a key effector molecule in migraine.[100] Released by perivascular sensory fibers, it contributes to vasodilation, mast cell degranulation, neurogenic inflammation, and possibly peripheral pain sensitization in migraine.[101] As a neurotransmitter in the trigeminal nucleus caudalis, it contributes to central sensitization.[102]

In addition, however, CGRP reduces oxidative stress in the body,[103] in part by lowering the expression of the enzyme, NADPH oxidase, which produces superoxide,[104] and in part by increasing the activity of antioxidant enzymes.[103] Further, CGRP prevents apoptosis under oxidizing conditions.[105] Moreover, like activated platelets, CGRP facilitates wound healing and tissue repair in the body, in part by increasing the expression of VEGF, bFGF, and TGF-β.[101] Indeed, a loss of CGRP-containing sensory nerves may account for some of the impaired wound healing seen in diabetes.[101]

In the endothelium, CGRP antagonizes the oxidant-inducing effects of angiotensin II much as does nitric oxide.[101] In the brain, CGRP expression in neurons is upregulated by axonal damage, infection, and inflammation[106] and CGRP in turn activates astrocytes and microglia.[106,107] Moreover, CGRP is a strong vasodilator and, under ischemic conditions, activates the CREB transcription factor, and raises levels of bFGF and the protein Bcl-2, suppressing apoptosis of neurons.[108,109] Thus, CGRP is thought to be part of the central nervous system's response to ischemia, injury, and infection,[9,110-113] inducing repair.[106]

Accordingly, injection of CGRP directly into a cerebral ventricle improves learning and memory in rats,[114] increases neurogenesis and the expression of NGF in mice subjected to combined restraint and water immersion stressors,[115] and raises production of GDNF in a mouse model of amyotrophic lateral sclerosis.[106]

Indeed, CGRP has been used in two controlled human trials to reverse persistent neurological deficits, attributed to vasospastic ischemia, after aneurysm surgery.[116] In the larger trial, whose power was compromised by marked patient dropout due to systemic hypotension, the group receiving IV CGRP had numerically improved neurological outcome at 3 months (vs usual treatment) but this result was not statistically significant.[117] More recent animal studies have focused instead on the downstream neurotrophic factor, bFGF, which has been shown to markedly reduce infarct volume, neurological deficit, and the impaired activity seen following cerebral ischemia-reperfusion in rats.[118]

Cortical Spreading Depression.—In CSD, a wave of intense activation and reactive hyperemia spreads geographically over the surface of the cortex, followed in its wake by a depression of spontaneous neural activity, thought to correspond to the scintillations and scotomas, respectively, of migraine aura.[119] The propagation of CSD depends on the release of potassium ions and glutamate, which are thought to directly depolarize peripheral nociceptors, thereby initiating neurogenic inflammation and inducing a migraine.[119,120] Further, CSD entails the production of oxidants,[14] which can irritate nociceptors through the TRPA1 ion channel. Thus, CSD may be a key initiating event for the pain of migraine.

However, CSD is also a form of preconditioning, a minor stress that protects the brain against a subsequent, larger stressor.[121] Thus, in animal models and tissue slices, CSD is known to limit the amount of damage caused by subsequent ischemia.[122] In part, this seems to occur because CSD activates an enzyme, AMP-activated protein kinase (AMPK), that detects conditions of depleted energy and downregulates energy-demanding pathways.[122] CSD also induces the transcription of a number of antioxidant and neuroprotective genes.[123,124] Further, an increase in uncoupling protein-5 reduces the production of a key oxidant, superoxide, by the mitochondria following CSD.[124]

Moreover, the initial phase of CSD is a wave of depolarization and hyperemia. These increases in neural activity and blood flow should raise production of BDNF by neurons and the endothelium, respectively. In fact, BDNF mRNA and protein levels are markedly increased in the rat brain,[86,125-127] and long-term synaptic potentiation is strengthened,[128] following CSD.

Release of Serotonin.—Electrophysiological, neurochemical, and platelet studies suggest that the interictal period in migraines is characterized by a serotonin deficit, which is rapidly reversed during a migraine attack.[129] During a migraine, there is increased synthesis of serotonin, normalizing it to levels seen in nonmigraineurs,[130] increased firing in the region of the DRN[6,131] potentially bathing the brain in serotonin,[132,133] and serotonin is

Table 1.—Neuroprotective Properties of Migraine Components

Component	Direct Antioxidant	Induces Antioxidant Enzymes	↓ Oxidant Production	Releases Growth Factors	↑Stem Cell Proliferation	↑ Mitochondrial Biogenesis
Platelet Activation				√	√	
PPE	√		√	√		
Nitric Oxide		√	√	√	√	√
BDNF		√	√	√	√	
CGRP		√	√	√	√	
CSD		√	√	√	√	
Serotonin	√	√	√	√	√	√

released by blood platelets, increasing its plasma concentration.[134-136]

Serotonin may contribute to migraine pain by producing inflammation and sensitizing sensory nerves.[137] However, it is also involved in neuroprotection.

Serotonin has antioxidant properties in vitro[138] and an animal model of serotonin deficiency shows reduced antioxidant capacity.[139] Moreover, serotonin promotes the differentiation of neurons and glia, and the formation of synapses.[132,133] Acting through the 5-HT_{2B} receptor, serotonin facilitates neurogenesis in the dentate gyrus of the hippocampus.[140]

In part, serotonin seems to exert these neurotrophic effects by releasing a number of growth factors. Thus, via the 5-HT_{1A} receptor, serotonin appears to trigger the release of a protein, S100B, from astrocytes. S100B resembles a neurotrophic factor in that it prevents apoptosis, facilitates the outgrowth of neurites, and modulates long-term synaptic plasticity.[141] Moreover, serotonin causes astrocytes to raise their antioxidant support for neurons, by stimulating the release of metallothioneins, a class of antioxidant enzymes, and cysteine, which is taken up by neurons and used to produce the antioxidant glutathione.[141]

It appears that serotonin can also induce the production of BDNF, which as we have seen promotes neurogenesis, dendritic branching, synaptic plasticity, and neuronal survival (suppression of apoptosis) during ischemia, physical trauma, and psychosocial stress.[89,91,92] Further, serotonin can stimulate neurogenesis via insulin-like growth factor-1 (IGF-1)[142,143] and limit glutamatergic neurotransmission through the release of VEGF and fractalkine.[144-147]

Additional forms of neuroprotection might be suspected. Thus, in proximal tubular cells of the kidney, agonists at $5HT_2$ receptors stimulate biogenesis of mitochondria, and thus presumably recovery from ischemic and other injuries.[148]

Through these mechanisms, serotonin protects neurons from ischemic and excitotoxic injury.[149] All this may explain why blood levels of serotonin rise at the start of a migraine, as they do in closed head injury.[150] In animal studies, 5-HT_{1A} agonists such as buspirone decrease lesion size and improve behavioral and cognitive recovery after experimental head injury or subdural hematoma,[151] while in a clinical trial, fluoxetine, an SSRI and 5-HT_{1A} agonist, facilitated motor recovery following ischemic stroke, independently of effects on mood.[152]

The effects of these migraine components are summarized in the Table 1. As may be seen, each component is neuroprotective through multiple mechanisms.

Interaction Among Components.—These components appear embedded in feedback loops, as shown schematically in Figure 1. For example, PAF stimulates the release of BDNF and serotonin from platelets and increases production of nitric oxide by the endothelium,[153] which in turn raises production of BDNF. BDNF then furthers the production of nitric oxide in a positive feedback loop.[77,79] CGRP and substance P may stimulate eNOS and increase

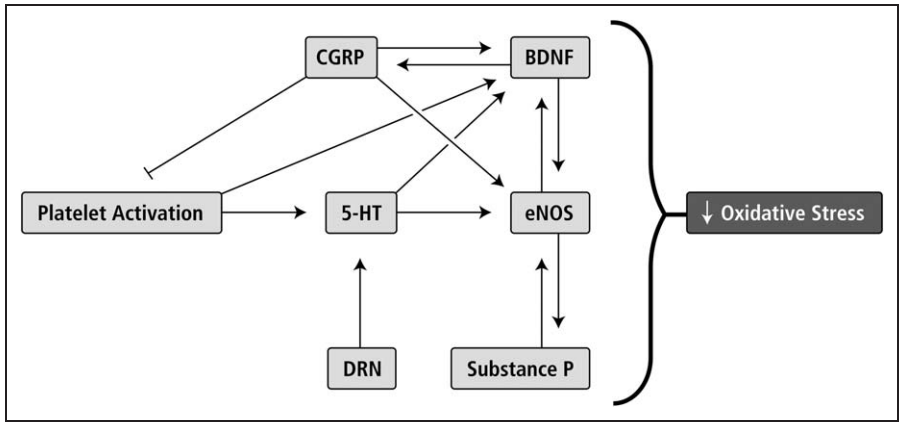

Fig. 1.—Interactions among migraine components. The components of a migraine attack are integrated by mostly positive, mutually reinforcing feedback loops. 5-HT = serotonin; BDNF = brain-derived neurotrophic factor; CGRP = calcitonin gene-related peptide; DRN = dorsal raphe nucleus; eNOS = endothelial nitric oxide synthase.

the production of nitric oxide.[154,155] Nitric oxide, in turn, may facilitate substance P release and, speculatively, CGRP neurotransmission in the trigeminal nucleus.[66,102] Serotonin, we have seen, stimulates endothelial nitric oxide production and activates a wide range of proliferative and prosurvival second messengers, including BDNF, VEGF, and IGF-1.

There are also indications of negative feedback loops, perhaps contributing to the self-limiting nature of migraine attacks. Thus, while PPE allows delivery of an antioxidant, albumin, to the CSF, in theory it could also allow entry of white blood cells, compromising the immune privilege of the CNS. However, at least in the mouse peritoneal cavity, CGRP attenuates the movement of neutrophils and monocytes through the endothelium,[156] perhaps because CGRP inhibits the endothelial cells from producing certain chemokines as well as macrophage chemoattractant protein-1 and vascular cell adhesion molecule-1.[101,157] Thus, CGRP, an effector molecule for neurogenic inflammation, helps to maintain the non-immune nature of the inflammation. CGRP also limits platelet activation,[158] presumably helping to prevent excessive coagulation. Serotonin, meanwhile, through the release of fractalkine,[159,160] and directly through 5-HT_{2C} receptors,[161,162] limits the activation of microglia, helping to prevent neurogenic inflammation from spilling over into classical inflammation.

Thus, the suggestion is of an integrated system for neural protection and repair, coextensive with migraine.

DISCUSSION

Numerous components of the migraine attack—CSD, platelet activation, PPE, generation of nitric oxide, the release of CGRP, BDNF, substance P, and serotonin—and, we may surmise, the migraine itself—appear to be neuroprotective, reducing oxidant production and the energy requirement of neurons, stimulating neurogenesis, causing mitochondria to replicate, and delivering antioxidants and, especially, growth factors to the brain.

Nonetheless, the approach here—speculative, hypothesis-generating, preliminary—has a number of potential weaknesses:

First, the literature reviewed on the components of migraine was in vitro or on conditions other than migraine, primarily ischemia. The components may not have the same effect in the context of a migraine attack. However, ischemia may not be a far-fetched analogy, as migraines may be triggered by hypoxia,[20] hypoglycemia,[20] and presumably via CSD, by microembolisms,[163,164] all aspects of ischemia. Moreover, the fact that numerous components of a migraine effectively respond to a threat to the brain such as ischemia is consistent with the idea that primary migraine is also a response to threats to the brain.

Second, it must be considered that neurotrophic pathways are pleiotropic; the mere fact that they are activated does not mean that they will have a neuroprotective effect in migraine. We have seen, however, that at least in ischemia, the activation of these pathways does seem to be protective.

There are, in addition, arguments against *any* neuroprotective theory of migraines. Thus, high baseline attack frequency[165] and relative failure of acute medications[166] predict new-onset chronification, suggesting that migraines are progressive. Moreover, the frequency of migraine attacks and the duration of the disorder predict harm to the brain,[167] while in migraine with visual aura, the associated white matter lesions progress over time.[168] Further, migraine disorder increases the risk of conditions such as hypertension,[169] ischemic stroke,[170] myocardial infarction[171,172] and, of note, Parkinson's disease.[173] How can such a broad swath of damage be reconciled with a neuroprotective process?

Relevant here is that neurotrophic signaling is bivalent.[174] That is, while BDNF, for example, is generally neuroprotective through the TrkB receptor, under certain circumstances BDNF can have the opposite effect. Thus, when neurons are subjected to severe mechanical stresses (as in traumatic brain injury), severe biochemical stresses (such as amyloid beta in Alzheimer's disease) or, apparently, severe psychosocial stress (as in major depressive disorder and posttraumatic stress disorder), they over-express a low affinity neurotrophin receptor, $p75^{NTR}$, through which BDNF is pro-apoptotic and inhibits the proliferation of stem cells.[175] That is, high levels of physiological or psychosocial stress may connote an environment so harsh or damage so severe that apoptosis seems the best option. Under these conditions, a migraine attack could be neurodestructive. Similar to other stress-related disorders, processes that are adaptive under normal circumstances may become harmful under high allostatic load—environmental pressures to which adaptation exerts a toll on the individual.[176] Thus, migraines may resemble other defensive reactions such as fever, swelling, inflammation, and pain—promoting healing at moderate levels but causing damage when too intense.

This harm could occur through several other mechanisms. First, we have seen that CSD protects the brain during subsequent ischemia-reperfusion. However, when CSD follows traumatic brain injury, ischemic stroke, subarachnoid hemorrhage, or eliptiform activity, the combination of oligemia and high energy demands to restore ion homeostasis are thought to cause (further) ischemic damage.[177] These models differ from migraine in that they involve damaged tissue with impaired neurovascular coupling. In healthy tissue, as presumably characterizes migraine, CSD appears to be neuroprotective. Possibly, however, in small regions of cortex the vascular supply might be inadequate for the energy demands of CSD, causing localized ischemic damage. This might account for the progression of white matter lesions in migraine with aura.

Second, the combined presence of neurotrophic factors and nociceptive drive may lead to synaptic strengthening in pain pathways and conversion to a chronic disorder.[86] As only 2.5% of migraineurs transition to the chronic state in a given year,[178] this presumably describes only the most severe migraines.

Third, under some conditions migraines might increase oxidative stress in a vicious cycle. Thus, mast cells can raise the production of oxidants by the brain's renin-angiotensin system.[179,180] Activated platelets can produce oxidants by forming complexes with leukocytes.[181] Moreover, PPE is a means by which neurogenic inflammation (neuroprotective) can trigger classical inflammation, causing further oxidative damage.[182] We have seen that at moderate levels, albumin extravasated into cerebrospinal fluid likely functions as an antioxidant, facilitates repair of neuronal membranes, and causes astrocytes to release a trophic factor, oleic acid. However, albumin in CSF also may cause the proliferation of microglia[183] and promote inflammation.[184] Naturalistically, a high concentration of albumin might indicate severe compromise of the blood-brain barrier and elicit a strong defensive response against pathogens.

Thus, the damage associated with migraine may be restricted to unusually intense, frequent, or prolonged attacks, migraines occurring in the context of severe physiological or psychosocial stress or, in the case of CSD, in regions of impaired vascular supply.

Alternatively, the damage may not be due to migraine attacks but to the migraine diathesis. The attacks may be simply a marker for the severity and persistence of the underlying diathesis. Consider, for example, the increased risk of hypertension in migraineurs. In animal models, CGRP,[185] eNOS,[67] and serotonin[186] each protect against the development of hypertension. However, oxidative stress, a likely aspect of migraine vulnerability, is a risk factor for hypertension,[187] endothelial dysfunction,[188] and atherosclerosis.[189]

Thus, the contention here is that to truly solve migraines and the associated risk, we must identify and treat the underlying diathesis, rather than focusing on the body's defensive response to it.

Currently, CGRP is a promising therapeutic target in migraines.[190] Thus, the evidence that CGRP may have a neuroprotective function raises the possibility, theoretical at this point, of long-term harm from anti-CGRP medications.[109,191]

CONCLUSIONS

In all, then, there seems a fair amount of evidence that numerous components of a migraine attack, and presumably the attacks themselves, involve processes that protect and repair the brain. Of course, the existence of an integrated neuroprotective, neurorestorative system could be quite valuable, and would continue the grand tradition of migraines as a Rosetta stone,[192,193] illuminating normal brain functioning as well as disease, and informing the broad neurological field. For intrinsic to the human condition is a brain that must balance between sensation and excitotoxicity, between defense against pathogens and unintended self-destruction, and between receptivity to the environment and exposure to its toxins. The migraine attack, as a particularly violent return to homeostasis, may have a key role in maintaining our neural integrity.

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