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Review Articles

Migraine Triggers and Oxidative Stress: A Narrative Review and Synthesis

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Background.—Blau theorized that migraine triggers are exposures that in higher amounts would damage the brain. The recent discovery that the TRPA1 ion channel transduces oxidative stress and triggers neurogenic inflammation suggests that oxidative stress may be the common denominator underlying migraine triggers.

Objective.—The aim of this review is to present and discuss the available literature on the capacity of common migraine triggers to generate oxidative stress in the brain.

Methods.—A Medline search was conducted crossing the terms "oxidative stress" and "brain" with "alcohol," "dehydration," "water deprivation," "monosodium glutamate," "aspartame," "tyramine," "phenylethylamine," "dietary nitrates," "nitrosamines," "noise," "weather," "air pollutants," "hypoglycemia," "hypoxia," "infection," "estrogen," "circadian," "sleep deprivation," "information processing," "psychosocial stress," or "nitroglycerin and tolerance." "Flavonoids" was crossed with "prooxidant." The reference lists of the resulting articles were examined for further relevant studies. The focus was on empirical studies, *in vitro* and of animals, of individual triggers, indicating whether and/or by what mechanism they can generate oxidative stress.

Results.—In all cases except pericranial pain, common migraine triggers are capable of generating oxidative stress. Depending on the trigger, mechanisms include a high rate of energy production by the mitochondria, toxicity or altered membrane properties of the mitochondria, calcium overload and excitotoxicity, neuroinflammation and activation of microglia, and activation of neuronal nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. For some triggers, oxidants also arise as a byproduct of monoamine oxidase or cytochrome P450 processing, or from uncoupling of nitric oxide synthase.

Conclusions.—Oxidative stress is a plausible unifying principle behind the types of migraine triggers encountered in clinical practice. The possible implications for prevention and for understanding the nature of the migraine attack are discussed.

Key words: TRPA1, migraine, triggers, oxidative stress, antioxidants

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In clinical experience and patient report, acute migraine attacks are precipitated by a wide range of factors[1,2] – behavioral (eg, stress, mental overwork, irregular sleep), environmental (eg, noise, odors), dietary (eg, alcohol, nitrates), and pharmacological (especially nitroglycerin). On a practical level, identifying trigger factors may help in treatment[3] by preventing some migraine attacks, imparting a sense of control to the patient, and providing advanced warning that allows for early use of acute medication.[4–6]

On a theoretical level, triggers raise intriguing questions about the nature of migraines. Clinically,

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triggers seem to summate, with a migraine resulting when a threshold is breached.[7,8] In the laboratory, isolated triggers tend to have less effect than exposure to several triggers in succession.[9] This implies that triggers are converging on a common pathway, but the mechanism by which, for example, mental effort, hot dogs, diesel fumes, psychosocial stress, and aged cheese interact calls for explanation.

One approach to the theory of triggers arises from the pathophysiology of migraine. Triggers are understood by their capacity to constrict or dilate blood vessels, directly irritate peripheral nociceptors, or activate a hyperexcitable cortex, either directly, or by interacting with modulatory serotonergic and noradrenergic brainstem nuclei.[10–15]

A second approach, more teleological, was given by Blau,[16] who noted that migraine triggers tend to be exposures that in higher amounts would damage the brain – hypoxia, hypoglycemia, alcohol, and environmental extremes (eg, of heat or cold) being prime examples. This is consistent with Loder's observation that the high prevalence of migraines implies that they, or the genes that underlie them, confer an evolutionary advantage.[17] How this would extend to noise or mental effort, however, is less clear. Moreover, the physiological pathways by which potential harm generates a migraine require explication.

As noted by others,[18] the recent discovery of the TRPA1 ion channel in nociceptors suggests one possible explanation. In animals, calcitonin gene-related peptide (CGRP) can be released from dural afferents, promoting neurogenic inflammation, pain sensitivity, and behavioral evidence of a migraine, by agonists of the TRPA1 channel.[18] Thus, Dussor et al note that a number of irritants well known to be migraine triggers (eg, formaldehyde[19]) are in fact activators of the TRPA1 channel.[20]

Particularly important for our purposes is that the TRPA1 channel is specifically activated by oxidative and nitrosative stress.[21] A mechanism for sensing such conditions would surely have adaptive significance, as the brain is uniquely susceptible to oxidative damage.[22] Long-term exposure to oxidative stress has been suspected of playing a causal role in a range of brain pathologies.[23] The function of the TRPA1 channel raises the possibility that migraine triggers might have in common that they induce oxidative stress in the brain, as suggested by Benemei et al.[18]

Despite this conceptual advance, there has not yet been a comprehensive consideration of the types of migraine triggers found in clinical practice in relation to oxidative stress. In what follows, we will briefly review the main sources of oxidative stress in the brain and then consider how these sources are affected by the various migraine triggers, drawing on *in vitro* and animal data.

Oxidative Stress.—By losing an electron or a hydrogen atom, a molecule is oxidized and becomes capable of oxidizing the molecules it encounters. Examples of oxidants are free radicals such as peroxynitrite ($ONOO^{\bullet}$), the peroxyl radical ($ROO^{\bullet}$), the hydroxyl radical ($OH^{\bullet}$), and the superoxide anion ($^{\bullet}O_2^-$). There are also nonradical oxidants, those that do not have charges, such as hydrogen peroxide (H_2O_2) and hypochlorous acid (HOCl; bleach).

Certain oxidants (eg, H_2O_2), in controlled amounts, are physiologic and have important signaling functions within the cell.[24,25] However, when oxidants are produced in excess or when the antioxidant defenses that regulate them are compromised, the result is oxidative stress, a condition in which biomolecules such as DNA, membrane lipids, enzymes, and structural proteins can be damaged through oxidation to an extent that exceeds repair capacity.[26] Oxidative stress is thought to contribute to a wide range of diseases.[25]

Sources of Oxidants.—There are three broad endogenous sources of oxidants in the brain: (1) *Mitochondria*. Based on animal data, between 0.1% and 4% of electrons ordinarily leak from mitochondrial complexes I, III, and possibly II, generating superoxide anions.[27–29] Impediments to the smooth flow of electrons through the respiratory chain can increase their leakage and reaction with oxygen to form superoxide. Thus, damage to the structure of mitochondria, accumulated mutations of mitochondrial DNA, and mitochondrial toxins such as rotenone and cyanide, lead to increased formation of superoxide.[30,31] (2) *NADPH oxidase*. Oxidative

stress plays a key role in host defense, particularly the bactericidal function of white blood cells.[32] The superoxide radical is produced by the NADPH oxidase (NOX) enzymes and converted into hydrogen peroxide in macrophages and hypochlorous acid in neutrophils.[32] In the brain, one form of NOX enzyme, NOX2, is found on neurons, astrocytes, and microglia,[33] where it is activated by bacteria, toxins, and other threats.[32] (3) *Other enzymes*. For certain enzymes, oxidants are a byproduct of the reactions they catalyze. A key example in the brain is monoamine oxidase (MAO), whose role is to metabolize monoamines such as dopamine, norepinephrine, and serotonin, but which produces hydrogen peroxide in the course of the reaction.[34] Certain cytochrome P450 enzyme systems that metabolize xenobiotics and drugs also produce oxidants as a byproduct.[35]

Antioxidant Defenses.—Oxidants are deactivated, that is, reduced, by certain enzymes and by nonenzymatic antioxidants. Major examples of antioxidant enzymes are superoxide dismutase, catalase, glutathione peroxidase, and peroxyredoxins. Examples of nonenzymatic antioxidants are glutathione and ubiquinone (coenzyme Q10), both of them endogenously generated and, solely from the diet, ascorbic acid, alpha-tocopherol, and beta carotene.[36] In particular, glutathione is the main nonenzymatic antioxidant found in cells.[22,37] It is easily oxidized, protecting protein thiol (R-SH) groups from oxidation. It is regenerated in cells by the glutathione reductase enzyme. For oxidative damage that has already occurred, the body has a number of compensatory and repair processes. For example, an enzyme, apurinic endonuclease (Ape1), activates the base excision repair pathway, correcting common types of oxidative damage to DNA.[38]

Migraines and Oxidative Stress.—Migraine may be associated with increased vulnerability to oxidative stress. Some migraineurs, particularly those with white matter hyperintensities on MRI and/or who have a family history of migraine, show decreased activity of catalase in the serum, measured interictally,[39,40] and thus may have difficulty detoxifying hydrogen peroxide. Lower activity of superoxide dismutase has been found in the erythrocytes[41] and platelets[42] in migraine, as has a lower activity of glutathione peroxidase in erythrocytes,[41] and lower total antioxidant capacity and nonoxidized thiol concentration in serum.[43]

Migraine Triggers.—Thus, oxidants arise endogenously in the brain from a number of sources. In excess amounts, they are potentially harmful. We have seen that the brain has ion channels that can detect oxidative stress, triggering neurogenic inflammation. It is plausible that migraine triggers have in common a capacity to increase oxidative stress. In what follows, we will consider this possibility for a range of migraine triggers.

Here, we will use the term "trigger" to mean an external or internal exposure that increases the probability of a subsequent migraine attack. Because the association is probabilistic and additive, "potentiating factor" is a more accurate description. However, we will retain the term "trigger" due to its simplicity and nearly universal use in the migraine literature.

METHODS

A Medline search was conducted by the author crossing the terms "oxidative stress" and "brain" with "alcohol," "dehydration," "water deprivation," "monosodium glutamate," "aspartame," "tyramine," "phenylethylamine," "dietary nitrates," "noise," "weather," "hypoglycemia," "hypoxia," "infection," "estrogen," "circadian," "information processing," "psychosocial stress," or "nitroglycerin and tolerance." The reference lists of the resulting articles were examined for further relevant studies. The search was restricted to English language articles published between 1990 and 2014. Studies were included in the review if they examined the exposure as a single intervention and reported empirical data on whether and/or by what mechanisms the exposure induced oxidative stress. *In vivo* studies were selected when available. Studies were preferred if they reported on exposures plausible for daily life (eg, studies of acoustic trauma from blast injuries were excluded for "noise"). In seven cases, no relevant articles were found and the searches were modified as follows: "tyramine and oxidative and brain," "information processing and oxidative stress," "nitroglycerin and tolerance and oxidative stress," "monosodium glutamate and neurotoxicity," "sleep

deprivation and oxidative stress and brain," "air pollutants and oxidative stress and brain," and "nitrosamines and oxidative stress and brain." For flavonoids, the search "flavonoids and prooxidant" was used to exclude the very large number of studies examining the antioxidant effects of flavonoids. Because noninvasive measures of oxidative stress in a living brain are not yet available, the studies were generally of *in vitro* or animal data.

RESULTS

The number of search results vs retained studies were: dehydration (4/1), water deprivation (5/1), aspartame (7/4), phenylethylamine (7/2), nitrosamines (7/1), noise (44/1), hypoglycemia (52/2), psychosocial stress (12/1) and, for the modified searches, tyramine (27/5), monosodium glutamate (49/1), air pollutants (42/2), sleep deprivation (42/2), and information processing (38/1). For hypoxia (897 results), alcohol (296), infection (244), estrogen (135), flavonoids (112), and nitroglycerin (72), numerous studies were available reporting the same mechanisms. For these triggers, between 1 and 4 illustrative papers were retained.

Dietary Triggers

In 1674, Thomas Willis cited "errata in victu," errors in diet, as eliciting factors in cephalalgia (Willis, 1674, cited in Living, 1873).[44] In modern times, nutritional factors consistently turn up in migraineurs' reports, although the proportion of patients with prominent alimentary triggers may be small.[1,4,45] Several dietary components in particular have been suspected:

Alcohol.—Long-term exposure to high doses of alcohol, as seen in chronic alcoholics, leads to loss of frontal lobe volume, diffuse white matter atrophy, and mild dementia.[46] Even adolescents and young adults with alcohol use disorders show impairments in executive functioning that resemble premature aging, and neuroimaging studies suggest loss of volume of prefrontal cortex and the hippocampus.[47] In animal studies, a single day of alcohol consumption, analogous to a binge, is sufficient to cause neural degeneration and reactive gliosis.[48] The brain damage in alcohol is thought to be mediated by oxidative stress from several sources.

Alcohol is metabolized in the body in part by cytochrome P450-2E1 (CYP2E1) and in part by alcohol dehydrogenase. Superoxide and hydrogen peroxide are byproducts of CYP2E1 functioning.[35,49] Some of this enzyme is located within the mitochondria, where oxidative damage could promote further oxidant production through the leakage of electrons from complexes I and III.[50] Moreover, CYP2E1 is inducible – exposure to a substrate such as ethanol prevents its proteosomal degradation, causing an increase in the amount of the enzyme within the cell.[35,50]

For both CYP2E1 and alcohol dehydrogenase, a metabolite of alcohol is acetaldehyde, a toxin that activates inducible nitric oxide synthase, xanthine oxidase, and neuronal NADPH, causing further production of oxidants.[49] In addition, high doses of alcohol activate microglia, markedly increasing the production of reactive oxygen species.[51]

The fluidity of mitochondrial membranes is affected acutely by ethanol, leading to altered enzyme function, leakage of electrons, and increased oxidant production.[52] This in turn is thought to oxidize the membranes further, causing increased oxidant production in a vicious cycle.[53]

Moreover, as a diuretic, alcohol induces a compensatory release of arginine vasopressin.[54,55] As will be discussed further when we consider water deprivation, vasopressin increases superoxide release by the vasculature.[56]

Alcohol is often cited by patients as among the most prominent dietary triggers.[45,57] It is plausible that this reflects the numerous ways in which alcohol generates potentially toxic levels of oxidative stress in the brain.

Water Deprivation.—Water deprivation is supported as a migraine trigger by retrospective report[58] and case studies.[59,60] In mice, dehydration increases the concentration of arginine vasopressin in the plasma, through increased production by the hypothalamus and because plasma volume is lower.[56] Vasopressin, in turn, releases endothelin which, acting through the endothelin A receptor, raises the production of superoxide anion by the vasculature. The resulting oxidative stress is marked enough to impair cerebrovascular reactivity and autoregulation.[56]

Monosodium Glutamate.—Some support for a general monosodium glutamate (MSG) syndrome, including headache, muscle tightness, numbness, weakness, and flushing, is found in two double-blind, placebo-controlled trials.[61,62] Both trials used high doses (up to 5 g) on an empty stomach in people self-identified as sensitive to MSG. In both cases, the presence of symptoms was dose-related but the reproducibility of individual symptoms was low.[63]

MSG that reaches general circulation appears to raise brain levels of glutamate.[64] There, it stimulates ionotropic and metabotropic glutamate receptors on neurons, causing calcium influx. This increases the neurons' rates of oxidative phosphorylation to provide the energy for restoring ion homeostasis, which in turn raises oxidant production. There can also be uptake of calcium by the mitochondria, causing transient opening of permeability transition pores and consequent further release of superoxide anion.[64]

When glutamatergic stimulation is at normal physiological concentrations, the resulting oxidative reactions likely play a role in synaptic plasticity, learning, and memory, and the collateral DNA damage is readily repaired.[65] At supraphysiologic concentrations, however, such as when the glutamate comes from an exogenous source, the excessive signaling and calcium influx leads to excitotoxicity: damage, necrosis, and/or apoptosis from oxidative stress.[64]

In most cases, it seems doubtful that MSG added to food significantly raises the levels in general circulation. In Western diets, approximately 10 g of glutamate is consumed daily as a normal constituent of protein and added MSG (≈0.6 – 2.3 g/day) is within the range of dietary variation. Moreover, of ingested glutamate, 95% is used by the enterocytes lining the intestines as a source of energy and for synthesis of glutathione.[63] However, normal dietary levels might not be benign to sensitive individuals. Foods naturally high in free glutamate, such as citrus and processed meats, figure high in the list of reported migraine triggers.[66]

Aspartame.—Aspartame consists of two amino acids, phenylalanine and aspartic acid, bound together as a methyl ester. Because it is 180 times sweeter than sucrose, amounts too small to contribute calories can be used to sweeten foods and beverages.[67] Some[68,69] but not all[70] double-blind, placebo-controlled trials have found depression and subtle cognitive impairments with high intake over 1–2 weeks, implying an effect on the brain.

One avenue by which aspartame might have neural effects is through the methyl ester linkage, which is metabolized by the body into methanol. The methanol, in turn, is metabolized by the alcohol dehydrogenase system into formaldehyde and then to formate.[67] Methanol, formaldehyde, and formate are all neurotoxins, as is well known from the blindness (from retinal and optic nerve damage) in people consuming methanol during Prohibition.[71] Formate inhibits mitochondrial complex III, causing release of superoxide, peroxyl, and hydroxyl radicals.[72] Methanol freely passes through the blood-brain barrier.

Further, a portion of the methanol is metabolized through an alternative, microsomal oxidizing pathway that creates as a byproduct, free radicals.[72] Moreover, in the liver and presumably the brain, enzymatic detoxification of methanol consumes glutathione, directly impairing antioxidant defenses.[72,73] Thus, in rats fed high doses of aspartame there are signs of oxidative stress and a compensatory increase in antioxidant enzymes in the cortex and other brain regions.[22,74]

Another source of neural effects may be excitotoxicity: Aspartame is metabolized into phenylalanine (50%) and aspartic acid (40%), as well as methanol (10%).[75] Brain levels of aspartic acid increase acutely after aspartame ingestion.[67] Aspartic acid is a precursor of glutamate and also a direct agonist at NMDA receptors.[67] This presumably causes enhanced glutamatergic signaling and excitotoxicity.[67] A third mechanism, seen over a 2-week period, is activation of microglia with resulting production of nitric oxide and other inflammatory mediators.[76] The nitric oxide, in turn, would lead to oxidative stress via the peroxynitrite radical.

Consistent with this evidence of oxidative stress and impact on the brain, some[77,78] but not all[79] double-blind, placebo-controlled trials have suggested a migraine triggering effect of aspartame.

Tyramine.—Tyramine is found in red wine and aged cheese. It first came under suspicion as a migraine trigger from the headaches reported by people who ingested these foods while taking MAO inhibitors, and from evidence that male migraineurs may have constitutively lower platelet MAO activity.[80] Migraine without aura is associated with higher plasma levels of octopamine and synephrine – metabolites of tyramine – suggesting that baseline levels of tyramine may be elevated.[81] Tyramine has been supported as a migraine trigger in several double-blind, placebo-controlled trials, nearly all from Hanington's laboratories,[82,83] but there have been negative results as well.[84] Only about 5% of migraineurs are thought to be sensitive to tyramine.[85]

In the brain, tyramine is endogenously produced, has receptors (trace amine-associated receptors),[86] and seems to function by modulating the effects of dopamine.[87] In particular, tyramine is indirectly sympathomimetic and both facilitates dopamine release and interferes with its reuptake.[88]

Tyramine is degraded by MAO, types A and B, found on the outside surface of the outer membrane of mitochondria. A byproduct of this reaction is hydrogen peroxide[87,89] in amounts far exceeding the background production by mitochondrial respiration.[90] Although MAO metabolizes other monoamines as well, such as dopamine and serotonin, at least *in vitro* the amount of hydrogen peroxide generated from tyramine is far greater than from dopamine or serotonin.[91] Tyramine, in fact, seems to be a source of oxidative damage to mitochondrial DNA.[92]

A caveat is that under normal circumstances, tyramine does not cross the blood-brain barrier.[87] Thus, if tyramine sensitivity is centrally mediated, it would require a disruption of the blood-brain barrier, such as from an inflammatory process, in dietary migraineurs. In fact, there is some indication that the blood-brain barrier is compromised interictally in migraine[93–95] although the evidence is inconsistent and of uncertain interpretation.[96,97]

Phenylethylamine.—β-phenylethylamine, a biogenic amine derived from phenylalanine, is a suspected active ingredient in such possible migraine trigger foods as chocolate, wine, and some cheeses.[98] Also, phenylethylamine is a minor metabolite of phenylalanine, of which aspartame is a significant source.[22] Phenylethylamine functions as an excitatory neuromodulator, and with acute administration it potentiates dopamine release and increases motor behavior.[98] It is also a norepinephrine and dopamine reuptake inhibitor.[99]

With long-term administration or at high doses, however, it inhibits complex 1 of the mitochondria in the dopamine-containing cells of the substantia nigra, leading to release of hydroxyl radicals, oxidative stress-mediated damage, and Parkinsonian symptoms in laboratory animals.[98,100] In fact, at high doses, β-phenylethylamine behaves similarly to rotenone and MPTP, used as neurotoxic models of Parkinson disease.[98]

Nonetheless, β-phenylethylamine has not been established with certainty as a migraine trigger. Other constituents, particularly the flavonoids in chocolate and wine may be the true culprit.[101,102] And the flavonoid content of chocolate and wine is generally considered anti-inflammatory. However, there are circumstances in which flavonoids may also generate oxidative stress, as discussed in the next section.

Flavonoids.—The case for flavonoids as a migraine trigger is circumstantial: They are found in fairly high quantity in the likely trigger foods red wine and citrus, they inhibit an enzyme (phenolsulphotransferase) that degrades catecholamines, and one class in particular, isoflavones, has weak estrogenic properties.[4]

Although pure flavonoids, without a glucose moiety, are clearly antioxidants *in vitro*, the functioning of flavonoids in the body, where they are subject to extensive metabolic processing, is not known with certainty.[103] Indeed, it may be through pro-oxidant properties that flavonoids are able to induce cell-cycle arrest and apoptosis in cancer cells.[104,105] Their antioxidant effects *in vivo* may be indirect, by inciting increased expression of antioxidant and detoxifying enzymes.[24]

What does seem clear is that flavonoids function as pro-oxidants under three circumstances: high concentration,[103] oxidation by intracellular

enzymes such as myeloperoxidase,[106] and when in contact with transition metals such as iron and copper.[107] Ordinarily, iron and copper are bound to proteins (eg, hemoglobin, ferritin for iron, ceruloplasmin for copper) that prevent this effect but free iron or copper may exist in the body after injury or in disease states.[103]

In fact, increased nonheme iron has been found in the periaqueductal gray,[108] red nucleus, putamen, and globus pallidus[109,110] in migraine. In theory, oxidative damage from repeated activation, hyperoxia, and perhaps nociceptive input itself may cause the buildup of iron and underlie the transition from episodic to chronic migraine.[111] In the event that some of this increased iron is free, that is, not sequestered in ferritin or by microglia, then it could catalyze flavonoids locally into pro-oxidant derivatives.

Nitrates.—Dietary nitrites, found in cured and processed meats, first emerged as a migraine trigger in a 1972 single-blind case study,[112] later confirmed in a small double-blind, placebo-controlled trial.[113] There has been only occasional confirmation since then, for example,[114] perhaps because the level of nitrate added to meats has declined markedly since 1972.[115]

The mitochondria, and certain enzymes (eg, xanthine oxidase) and proteins (eg, myoglobin, an oxygen-binding molecule in the muscles) are all capable of transforming nitrite into nitric oxide. These pathways function mostly when oxygen levels are low, and serve to dilate blood vessels, slow metabolism, and prevent injury by free radicals.[116] Thus, dietary and endogenous nitrite plays a key physiological role and may function as an antioxidant. However, under certain conditions xanthine oxidase produces superoxide,[117] which transforms nitric oxide into the peroxynitrite radical, a source of oxidative stress.[118]

Alternatively, nitrates – which are abundant also in vegetables and thus the Mediterranean diet – might be innocent. Some other component of processed meats might be to blame, such as nitrosamines, a reaction product of nitrates with protein, which have been linked to brain cancer in animal and some[119] but not all[120] epidemiological studies. *In vitro*, nitrosamines cause oxidative stress, including increased levels of oxidative DNA damage and 4-hydroxynonenal).[121] Because nitrosamines seem to cross the blood-brain barrier[122] it is possible this same effect occurs *in vivo*.

Environmental

Noise.—Exposure to noise seems to increase the probability of a migraine the following day.[123] It is cited by patients as a trigger in retrospective surveys[45] and has been supported as a headache trigger in a controlled laboratory study.[124]

In young mice, moderate levels of noise (80 dB SPL, 2 hours per day for 6 weeks) leads to deficits in spatial learning and avoidance conditioning. The extent of these deficits is correlated with increased oxidative stress in the hippocampus, auditory cortex, and inferior colliculus.[125] How moderate levels of noise exposure produce such downstream effects is not clear, although presumably excitotoxicity is a reasonable hypothesis.

Weather and Pollution.—Certain broad weather patterns may increase or decrease the probability of a migraine.[123] Among specific meteorological variables, a wind speed greater than 38 km/hour ($\approx$24 miles/hour) has received particular support.[126] The explanation has not been fully worked out but wind speed may be a proxy for the amount of dust the air has picked up (particulate matter with diameter >2.5 μm).[127] Air pollution, and particulate matter specifically, increases the probability of hospitalization for headache.[128,129]

Epidemiological evidence links air pollution to neurotoxicity. For example, in Valcamonica, Italy, where there is a high level of ferromanganese pollution from local industry, ostensibly healthy adolescents show tremors and subtle deficits in motor dexterity and coordination, whose intensity is correlated with the degree of manganese exposure.[130] In highly polluted areas of Mexico City, auditory brainstem nuclei in children show aggregated alpha synuclein (the amyloid involved in Parkinson's disease and dementia with Lewy bodies) and markers of oxidative damage to proteins and DNA.[131]

The mechanism linking exposure to pollutants with neurotoxicity is not certain. However, the olfactory nerve consists of axonal projections from

the nasal epithelium to the olfactory bulb. Particulates can be transported along the axons, bypassing the blood-brain barrier, and cross the synaptic cleft into the brain parenchyma.[132] Based on *in vitro* evidence, the pollutants may activate microglial via toll-like receptor signaling, inducing an inflammatory response and oxidative stress.[133] Thus, the neurotoxicity of inhaled particulate matter (collected from a public park in Tuxedo, NY, and concentrated) is exacerbated in apolipoprotein E null rats, which are systemically prone to oxidative stress.[134]

Physiological

Hypoglycemia.—Hypoglycemia is regarded as a migraine trigger based on case reports, for example,[135] an experimental study,[136] the ability of fasting to produce a headache,[137–139] and triggering of migraines by glucose tolerance testing.[140] Migraine may occur only after blood glucose levels are renormalized.[135] In the glucose tolerance test, migraines typically occur 1 to 4 hours after glucose ingestion.

Extreme hypoglycemia leads to coma and death, while repeated severe episodes in type I diabetic patients are associated with atrophy of the cortex, especially the occipital and parietal lobes, hippocampus, and basal ganglia.[141,142] Animal studies suggest that very severe hypoglycemia in the brain is, initially, an excitotoxic state due to excessive glutamate release, leading to mitochondrial dysfunction and oxidative stress.[143] Far higher levels of oxidative stress follow the reintroduction of glucose, which activates nitric oxide synthase and neuronal NADPH oxidase and causes free radical-mediated death of neurons.[144] NADPH oxidase requires a steady supply of NADPH, which cannot be regenerated until glucose is restored.[144]

Hypoxia.—Hypoxia is a suspected migraine trigger based on the similarity of migraine to acute mountain sickness, increased risk of migraine from living at high altitudes, and a tendency found in a controlled trial.[145]

In animal models, intermittent hypoxia causes oxidative stress via mitochondrial dysfunction (the mitochondria cannot function efficiently without an adequate supply of substrates) and via NADPH oxidase.[146] In addition, in hypoxic cells, the xanthine oxidoreductase enzyme, which ordinarily helps dispose of purines, is cleaved to form xanthine oxidase.[117] Xanthine oxidase may help increase blood flow to ischemic tissue by producing nitric oxide through the reduction of nitrites and nitrates. However, depending on the microenvironment, xanthine oxidase also produces superoxide.[117]

Nitric oxide, of course, is usually produced by the nitric oxide synthases, using L-arginine and molecular oxygen as substrates and NADPH and tetrahydrobiopterin as cofactors. When the supply of oxygen is insufficient, however, the nitric oxide synthases become "uncoupled," producing superoxide instead of nitric oxide.[147]

Infection.—A sick day not due to headache may increase the duration of a subsequent headache,[123] suggesting a common pathway. In mice, systemic exposure to an inflammatory stimulus, bacterial cell wall lipopolysaccharides, can cause induction of NADPH oxidase lasting for 10 months or longer.[148]

Estrogen.—The relationship between estrogen and migraines is complex. That women have an approximately threefold greater risk of migraines, beginning at menarche, suggests that female sex hormones contribute to migraines.[149,150] In an animal model of induced neurogenic inflammation, estradiol intensifies vasodilation, CGRP expression, and migraine-like behavior.[151] However, for immediate triggering, the case is strongest for estrogen withdrawal, that is, the declining estrogen level seen perimenstrually and at the time of ovulation.[150]

The phenolic structure of 17β-estradiol confers to it antioxidant properties *in vitro*, particularly for scavenging hydrogen peroxide[152] but it is not clear that this is relevant *in vivo*.[153] Markers of oxidative stress in the plasma tend to peak during the late follicular and early luteal phases of the menstrual cycle,[154,155] perhaps because of the rapid proliferation of follicular or endometrial tissue,[154] and to fall during menstruation.

In the central nervous system, however, estrogen facilitates a number of protective processes. It limits oxidative damage by increasing the expression of Cu, Zn-superoxide dismutase,[156] and helps reverse extant damage by upregulating repair enzymes thioredoxin[157] and Ape1.[38] Estradiol also

inhibits apoptosis by increasing the expression of Bcl-2[38,158] and reduces neuroinflammation.[159] The reduced activation of microglia, in turn, should lower brain oxidative stress.

In vitro, estradiol prevents glutamate toxicity by downregulating the expression of AMPA- and NMDA-type glutamate receptors.[160] In animals, estradiol reduces infarct size following middle cerebral artery occlusion.[161]

On the whole, then, estrogen appears to be neuroprotective, with antioxidant, anti-inflammatory, antiexcitotoxic, and antiapoptotic actions *in vivo*. It is not known, however, whether the short-term physiological withdrawal of estrogen during the menstrual cycle is enough to reduce this protection and render cells vulnerable to oxidative stress.

Behavioral

Sleep Cycle.—John R. Graham included "sleeping late" among his "errors of living for migraineurs to heed,"[162] and "sleeping late," "oversleeping," "sleep disturbance," and "change in sleeping habits or sleep" figure prominently among the triggers nominated by patients.[1,2,45] Of course, the maintenance of stable biological rhythms is helpful for managing other conditions that involve the brain, such as bipolar disorder and dementia.[163,164]

Disruptions in the circadian rhythm by exposing animals to shifts in the light-dark cycle interfere with learning and with the retention and retrieval of memories.[165] Hippocampal functions are most readily affected but with increasing circadian disruption, cognition that depends on the prefrontal cortex or dorsal striatum is affected as well.[166] Anatomically, there is evidence for reduced neurogenesis.[167,168] Corticosterone levels may be directly elevated or the circadian disruption may potentiate the corticosterone response to laboratory stresses.[169]

Approximately, 10% of all gene transcription in the mouse shows circadian oscillation, suggesting regulation by clock genes.[170] In particular, the transcription of major antioxidant enzymes, including superoxide dismutase, catalase, glutathione peroxidase, peroxiredoxins, and sestrins, appears to be controlled by circadian clock genes.[171]

Sleep deprivation is associated with a depletion of reduced glutathione in the brain.[172] As we have seen, glutathione is the body's main nonenzymatic antioxidant and is utilized by the antioxidant enzyme glutathione peroxidase, which detoxifies the hydroxyl radical. In rats, cognitive deficits from sleep deprivation are prevented by antioxidants,[173] further tying the harm of sleep deprivation to oxidative stress.

Mental Overwork.—Living[174] noted that among migraine triggers, "and perhaps more certainly influential than any of them" were "mental emotion and excessive brain-work."

Whether triggering by excessive mental work can be explained by oxidative stress is not clear because little is known about whether information processing influences redox state. However, the neuron-like structures of the retina can be damaged by high intensity light exposure (phototoxicity)[175,176] as can the cochlea and upstream cortical structures by excessive noise (acoustic trauma);[125,177] this damage is specifically through oxidative mechanisms. Similarly, painful stimulation of the limbs in rats increases lipid peroxidation in sensorimotor cortex for days afterwards.[178] Excessive release of glutamate (excitotoxicity) and the catabolism of dopamine[179] are sources of oxidative stress.

Moreover, information processing by the cortex is associated with augmented power and with synchronization across cortical regions in the high frequency bands of the electroencephalogram (EEG), particularly the high gamma range (60–200 Hz).[180] Lower gamma band activity (30–60 Hz, especially around 40 Hz) is thought to reflect perceptual binding – the integration of stimulus features into a coherent percept or gestalt, integration across different sensory modalities, and the maintenance of items in working memory.[181] Higher gamma band activity is thought to reflect such higher functions as selective attention and motor planning,[181] and perhaps information processing in general.[180] Gamma band activity may be more intense, with stronger amplitude and decreased inhibition, in migraineurs, at least in response to visual stimulation.[182]

Physically, the correlates of power augmentation at higher EEG frequencies are higher neuronal firing rates and greater utilization of glucose and

oxygen.[180,183] In particular, gamma oscillations seem to reflect the very rapid, synchronized firing of a certain class of GABAergic, inhibitory interneurons, parvalbumin-expressing basket cells. Because this firing is extremely rapid, it entails enormous energy demands by ion pumps to restore the neuron to the resting state.[184] The basket cells are replete with mitochondria that appear to be functioning at full capacity during gamma oscillations.[184]

A very high metabolic rate may cause oxidative stress. We have seen that ordinarily, between 0.1% and 4% of electrons leak from mitochondrial complexes I and III, generating superoxide anions.[29] Thus, the amount of superoxide produced appears to be a linear function of metabolic rate. Moreover, with high firing rates, there is potential for transient overload of calcium ions in the neuron, increasing oxidant production further.[185] Thus, fast-spiking interneurons may be key sources of oxidative stress, contributing to aging and brain pathology.[185]

Stress.—In patient reports, stress is generally among the most important migraine triggers.[45,186] Even this may be an underestimate, as stress may have a 3- or 4-day delayed effect,[187] making its triggering less observable. It has been confirmed as a trigger in laboratory studies.[188] Although there are a large number of major life stresses, a common unifying characteristic is social loss.

In rats, being raised in isolation leads to cognitive (impaired sensorimotor gating) and behavioral deficits, as well as a depletion of glutathione in the striatum and cortex.[189] Psychosocial stress seems to activate the same cellular defense processes as infection or toxins, perhaps because stress is a warning of impending injury. In prefrontal cortex and the nucleus accumbens, psychosocial stress in rats causes a tremendous increase in NOX2 expression and markers of oxidative stress.[33,190] Of note, this effect appears to trigger the signaling pathway for hypoxia, that is, by hypoxia inducible factor-1.[191] Thus, the idea that social stresses are encoded, not by novel structures but by novel ways of activating evolutionarily preexisting structures[192] appears true on a molecular as well as a neural systems level.

Daily Hassles.—An analog to the minor but repeated stresses of daily life are perhaps the studies in which primates must repeatedly establish, challenge, or defend their place in the status hierarchy. This type of stress is not benign but associated with impairments in neurogenesis and dendritic branching and growth in the CA3 region of the hippocampus.[193,194] These types of changes are generally associated with oxidative stress.[33]

Daily hassles are supported as a migraine trigger in prospective diary[195] and single-subject[196] studies. Both the amount and temporal patterning of stress may be key.[197]

Pharmacological

Nitroglycerin.—Nitroglycerin, a nitric oxide releaser, is known to cause an immediate headache in susceptible individuals and, in migraineurs, a migraine after about 5 hours.[198] Nitric oxide is probably an antioxidant *in vivo*.[199] Nitroglycerin, however, also causes the production of superoxide by the aldehyde dehydrogenase enzyme and by vascular NADPH oxidase.[200,201] Moreover, nitric oxide reacts with superoxide approximately three times faster than does the detoxifying enzyme superoxide dismutase (reaction rate 6.7×10^9 $M^{-1}s^{-1}$ vs 2×10^9 $M^{-1}s^{-1}$),[33,118] forming the highly reactive peroxynitrite radical.[202]

The main findings in the Results section are summarized in the Table.

DISCUSSION

Thus, migraine triggers encountered in clinical practice are capable of generating oxidative stress. Mechanisms include a high rate of energy production by the mitochondria, toxicity or altered membrane properties of the mitochondria, calcium overload and excitotoxicity, neuroinflammation and activation of microglia, and activation of neuronal NADPH oxidase. For some triggers, oxidants also arise as a byproduct of MAO or cytochrome P450 processing, or from uncoupling of nitric oxide synthase. In turn, oxidative stress, transduced by the TRPA1 ion channel on C fibers, can initiate CGRP release and the neurogenic inflammation of migraine.

As a response to oxidative stress, migraines could confer a survival advantage, as suggested by Loder.[17] The brain is uniquely vulnerable to

oxidative damage because of its high metabolic rate, the polyunsaturated (easily oxidized) nature of neuronal cell membranes, and the presence of iron and copper ions, which can catalyze the formation of free radicals. Antioxidant resources and cellular repair capacity, requiring energy, are limited in the brain.[22] Further, apoptosis as a defense mechanism – simply deleting through programed death cells that have become too badly damaged[203] – is not a good option in the brain, as neurons generally cannot be replaced.

We have seen that migraineurs may be particularly susceptible to oxidative stress because of lower antioxidant defenses. Moreover, oxidative stress may help account for the relationship between cortical spreading depression (CSD) and the subsequent attack in migraine with aura. Pro-oxidants potentiate and antioxidants prevent CSD,[204] suggesting a common vulnerability. Moreover, CSD itself causes oxidative stress[205] and in theory might thereby trigger a migraine. Consistent with this, CSD also rapidly induces certain antioxidant defenses – glutathione-S-transferase 5, apolipoprotein E, and major prion protein precursor.[206]

Further, in animal studies, by inhibiting the enzyme glutamine synthase and the glutamate transporter on astrocytes, reactive oxygen species may increase the concentration of glutamate, contributing to an excitable brain.[207]

Nonetheless, the approach taken here is not without weakness. Nearly all of the migraine triggers we have discussed are from traditional case studies and retrospective reports by migraineurs, subject to misattribution, illusory correlation, and recall bias.[123,208] The determination of causality is notoriously difficult in naturalistic, uncontrolled observation.[209] It is possible that some putative migraine triggers are in fact nothing more than bystanders. Yet we have seen that physiologically, these putative triggers are far from innocent; all conform to Blau's dictum that in higher amounts they would damage the brain. Moreover, if the true proximal trigger is oxidative stress then individual triggers may be difficult to validate in the laboratory as the dose, combination with other triggers, state of antioxidant defenses, and state of pain thresholds (which may be raised by the novelty of being in a study) would all moderate the result.[210]

A second weakness is that triggers have multiple effects, of which only one, oxidative stress, has been discussed. Thus, for example, hypoglycemia increases plasma free fatty acids, changes neuronal ion homeostasis, and alters levels of dopamine and serotonin, all of which could play a role in migraine.[135] Many triggers can activate the sympathetic nervous system which, in large amounts, would threaten homeostasis.[211] Yet the capacity of oxidants to elicit neurogenic inflammation through the TRPA1 ion channel, and the relevance of oxidative stress to neuronal functioning and survival, make this a tempting unifying principle.

The broad parsimony of the theory is also a key weakness: In common with other theories of migraine triggers, it does not allow us to deduce why a particular combination of exposures would lead to a migraine in a particular person at a particular time. The gap between theory and moment-to-moment experience is large. A strength of the theory is that it indicates the types of variables that would need to be measured to bridge this gap: the level and sources of brain oxidative stress in response to trigger exposure.

Some triggers do not seem well explained by this model – in particular the triggering by pericranial pain such as from eye strain or myofascial problems at the upper neck.[123] It is possible that neck pain is actually a premonitory symptom and not a trigger.[212] Alternatively, however, there is *in vitro* evidence that capsaicin and H_2O_2 applied to dorsal root ganglion neurons, have a multiplicative effect in causing CGRP release.[205] Thus, we might speculate that TRPV1 channels, sensitive to inflammatory pain, and TRPA1 channels, sensitive to oxidative stress, interact.[213] In that event, pericranial pain might function to lower the threshold of oxidative stress needed to trigger a migraine.

A further weakness in the theory is that oxidative stress in the brain increases with age[214] while the prevalence of migraines declines.[215,216] Presumably, one would need to posit that the ability to detect oxidative stress, like perceptual acuity, declines with age, or that the mechanisms that transduce oxidative stress become desensitized as basal levels rise. There is evidence, for example,

that parthenolide, a component of feverfew and a partial agonist of TRPA1, desensitizes the ion channel over time.[217]

Alternatively, the migraine response itself might become impaired. The vasodilatory component may be curtailed by endothelial dysfunction and atherosclerosis.[216] Brainstem dopaminergic circuits, and the substantia nigra in particular, have been implicated in migraine,[218] and perhaps the decline of neurotransmission in these circuits accounts for the improvement in migraines.[219] In a case-control study, 64% of migraineurs recalled an improvement or resolution of migraines following onset of Parkinson disease.[220]

Moreover, because trigger escape and avoidance can never be perfect, we must ask why migraineurs do not show progressive brain damage over time. But perhaps they do. Chong et al report that age-related cortical thinning is accelerated in migraineurs.[221] That this may not be an effect of the attacks themselves is suggested by the independence of the decline from disease duration and migraine frequency. However, the physiological basis of cortical thinning is poorly understood. A second possibility is that migraines are neuroprotective, effectively countering oxidative stress, as discussed briefly below.

Conversely, viewing migraine triggers from the perspective of oxidative stress has a number of advantages. It is physiologically plausible via the TRPA1 ion channel. It brings unity to a wide variety of behavioral, environmental, dietary, physiological, and pharmacological exposures. It provides an explanation for how triggers can summate.

Moreover, this perspective on triggers links to the further simplification that a number of agents that reduce oxidative stress seem to function as migraine preventives, including vitamin E,[222] ginkgo,[223] melatonin,[224] butterbur,[225] feverfew,[226,227] coenzyme Q10,[228] and possibly alpha lipoic acid,[229] and vitamin C with[230] or without[231] pine bark extract. The efficacy of riboflavin, too, might be indirectly due to reduced oxidative stress:[232] Riboflavin is a coenzyme for glutathione reductase, an antioxidant enzyme, and in its reduced form can directly scavenge oxygen radicals.[233]

The suggestion here is that this is a class effect,[43,205] and that other antioxidants will similarly be effective.

Consistent with this, regular moderate aerobic exercise, which seems to increase antioxidant reserves in the brain,[234] may also attenuate the intensity or frequency of migraines.[235]

Similarly, frontalis muscle tension biofeedback, empirically supported for the prevention of migraines,[236] has been shown to reduce serum peroxides and raise levels of nitric oxide and superoxide dismutase in chronic migraine.[237] The mechanism is not clear, but as a relaxation technique, it might lower stress-related activity of NADPH oxidase.

(For migraine preventive medications, the case is less clear: Flunarizine,[238,239] propranolol,[240] and topiramate[241] appear to be antioxidants, either directly or by raising levels of antioxidant enzymes, while valproate[242] and amitriptyline[243] appear to be pro-oxidants.)

On a practical level, the idea that triggers function via oxidative stress raises the possibility that antioxidants, taken at the time of trigger exposure, could function as "acute preventives" or "preemptive therapy."[232,244] There is some preliminary evidence for this for ginkgo[245] and the combination of ginger and feverfew.[246] Indeed sumatriptan, in some respects a late-stage preemptive, scavenges superoxide and hydroxyl radicals *in vitro*[247] and may reduce levels of peroxynitrite *in vivo*.[248] However, such a role for antioxidants has not been established and requires further research.

Conceptually, triggers as sources of oxidative stress adds to the view of migraines as a defensive response designed to limit further exposure to the triggers. The acute environmental intolerances of photophobia, phonophobia, and osmophobia, the aversion to exertion and movement, and the temporary decline in mental status all fit with an adaptive purpose of migraines.[249]

Further afield, it raises the possibility that migraines might actively counter oxidative stress on a physiological level. A number of candidate processes can be adduced. In various tissues of the body, CGRP reduces the expression of NADPH oxidase,[250] increases the activity of antioxidant enzymes,[251]

Table.—Type and Strength of Evidence Linking Migraine Triggers to Oxidative Stress

Trigger	Sources of Oxidative Stress	Type of Evidence	Strength of Evidence
Dietary			
Alcohol	NOX2, microglial activation, CYP2E1, mitochondrial toxicity, vasculature	*In vitro*, animal human (indirect)	+++
Water deprivation	Vasculature	Animal	++
Monosodium glutamate	Excitotoxicity	Animal	++
Aspartame	Excitotoxicity, microglial activation, mitochondrial toxicity, microsomes, depletion of glutathione	*In vitro*, animal	+++
Tyramine	MAO	*In vitro*	+
β-Phenylethylamine	Mitochondrial toxicity	*In vitro*, animal	+
Flavonoids	Direct pro-oxidants under some circumstances	*In vitro*	+
Nitrates	Xanthine oxidase	*In vitro*	+
Environmental			
Noise	Unknown (? excitotoxicity)	Animal	++
Weather and pollution	Microglial activation	*In vitro*, animal	++
Physiological			
Hypoglycemia	NOX2, excitotoxicity	Animal	+
Hypoxia	NOX2, mitochondrial dysfunction, xanthine oxidase, nitric oxide synthase	Animal	++
Infection	NOX2	Animal	+++
Estrogen withdrawal	Loss of antioxidant and antiexcitotoxic properties	*In vitro*, animal	+
Behavioral			
Sleep cycle	Decrease in antioxidant enzymes, depletion of glutathione	Animal	++
Mental overwork	Mitochondria (oxidative phosphorylation)	Animal	+
Stress	NOX2	Animal	+++
Daily hassles	Unknown	Animal	++
Pharmacological			
Nitroglycerin	Indirect pro-oxidant under some circumstances	Animal	++

"Strength of Evidence" is based on the number of pathways by which a trigger generates oxidative stress and their likelihood of being relevant in daily life: (+++) = Multiple well-established mechanisms demonstrated *in vivo* at plausible levels of exposure; (++) = A single strong source of oxidative stress demonstrated *in vivo*, but with uncertain mechanism and/or a level of exposure higher than would be encountered in daily life; (+) = *In vitro* or limited *in vivo* data.
CYP2E1 = cytochrome P450-2E1; MAO = monoamine oxidase; NOX2 = NADPH oxidase-2.

decreases oxidative stress,[251] and prevents apoptosis under oxidizing conditions by stimulating growth-oriented intracellular signaling pathways.[252] It is tempting to suspect a similarly protective role for CGRP in the brain. Similarly albumin, released into the dura by protein extravasation in migraines, is the main antioxidant in plasma.[253] In the brain, albumin causes astrocytes to release oleic acid, which is neurotrophic.[254] Further, serotonin, released into the blood by platelets[255] and perhaps throughout the cortex by the dorsal raphe nucleus during a migraine,[256] may have neurotrophic properties,[257,258] and cause the release of other neural growth factors.[259] Platelet activation, which takes place in migraine[260] as it does in tissue injury, is neuroprotective and neurorestorative in an *in vivo* model of cerebral ischemia.[261]

Nonetheless, a neuroprotective role of migraines remains highly speculative at this point.

CONCLUSION

Regardless, we have seen that underlying each of the traditional migraine triggers is their propensity to generate oxidative stress. This suggests that the recent discovery of the TRPA1 ion channel and the indications of higher oxidative stress and/or lower antioxidant defenses in migraineurs allow us to posit a physiologically informed principle uniting seemingly disparate migraine triggers and suggest a mechanism for an evolutionary advantage of migraines.

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