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New Metabolic Theories of Migraine Pathogenesis

by Linda Peckel

Triggers known to precipitate migraine attacks include psychological and physiologic stress, lack of sleep, noise, as well as many components of diet and pharmacologic therapies.
A wave of recent research has begun to explore theories involving metabolic causes for migraine that promise new therapeutic directions and plausible strategies to prevent future migraines.

Migraine has been a known medical entity for centuries, and yet there is still little understanding of the underlying mechanisms. New research indicates that may be because efforts have focused largely on pathologies of the brain, when the origins of migraine may be initiated at a much broader cellular level in the endocrine system. Neurovascular mechanisms of migraine have long been studied, but new evidence suggests that migraine is very likely a type of energy-deficit syndrome with mitochondrial dysfunction that leads to a cascade of neurologic events.[1]

The advent of magnetic resonance spectroscopy (MRS) has allowed measurement of many substances involved in energy metabolism, including lactate, magnesium, and adenosine triphosphate, which have implications in the expression of migraine symptoms.[1,2] Studies using MRS have identified pathophysiology in the hypothalamus, thalamus, and brain-stem that support an endocrine etiology for migraine.[2]

A 2019 review by Gross et al[1] published in *Nature Reviews* explored this theory further, stating that recent clinical evidence "suggests that migraine is a response to cerebral energy deficiency or oxidative stress levels that exceed antioxidant capacity and that the attack itself helps to restore brain energy homeostasis and reduces harmful oxidative stress levels." The review described peripheral abnormalities of mitochondrial enzyme function and glucose metabolism and oxidative stress as specific responses to external triggers that can result in migraine in individuals who exhibit cerebral hyperresponsiveness and abnormalities of central sensory processing.[1-3]

"Several metabolic pathways are likely to be involved depending on the genetic profile of the patient," coauthor Jean Schoenen, MD, PhD, a clinician at the Headache Research Unit at Citadelle Hospital and Professor of Functional Neuroanatomy and Clinical Professor of Neurology at the University of Liege in Belgium told *Neurology Advisor*.

The Role of Triggers in Migraine Etiology

At least 95% of people with migraine have 2 or more common triggers, which has led to investigation of the metabolic link between them.[2] New research now traces the effects of triggers back to essential abnormalities in energy metabolism, according to Jonathan Borkum, PhD, a psychologist from the University of Maine who has studied migraine metabolism. "Certainly, the metabolic theory shifts the focus from the attack itself to the sequence of events, potentially beginning weeks beforehand, that culminate in an attack," he told *Neurology Advisor*.

The many triggers known to precipitate migraine attacks include psychological and physiologic stress, lack of sleep, noise, as well as many components of diet and pharmacologic therapies.[2,4] In a 2015 review,[4] Borkum observed that while practical recommendations to "avoid triggers" gave the patient some sense of control over the condition, "on a theoretical level, triggers raise intriguing questions about the nature of migraines." Triggers often culminate in a migraine when a threshold is breached, he wrote, with the most common unifying factor among the triggers being their "propensity to generate oxidative stress."[4]

Dr Borkum emphasized that oxidative stress is the central disruptive process in migraine metabolism, initiated by a decline in brain energy. "If it is severe enough, it causes neurons to start using glucose for energy rather than for regenerating their antioxidant defenses," he explained. "In migraineurs, the interictal period [between attacks] is characterized by progressive alterations in electrophysiology and in serotonergic neurotransmission, particularly in the dorsal raphe nucleus. These changes are then reset by the migraine attack," he said.

Therapeutic Implications

The potential for metabolic etiologies for migraine opens a whole new approach to treatment, particularly the opportunity to intervene much earlier in the process. "The metabolic theory of migraines shifts the focus from thinking of the migraine attack as a disorder that needs to be suppressed (as, for example, by a triptan or by the new [calcitonin gene-related peptide] blockers) to thinking of the attack as an attempt by the brain to restore homeostasis after a threat to its functioning," Dr Borkum said.

This new direction holds great promise for effective prevention strategies. "The metabolic facet of migraine pathophysiology explains why metabolic treatments can be effective for migraine prevention," Dr Schoenen pointed out. "Available metabolic treatments have a very favorable efficacy/adverse effect profile, contrary to most classic preventive antimigraine drugs. They should therefore be considered as first-line therapies in many adult migraineurs, and even more so in childhood and adolescent migraine. If not sufficiently effective, they can be combined with classic preventives. In future studies, the efficiency of metabolic therapy in migraine can be optimized by developing novel compounds and/or diets and by identifying patients with the most disturbed metabolic profile," he explained.

A metabolic understanding of migraine may also shift thinking about acute therapies. Dr Schoenen noted that, "Among acute migraine treatments, only caffeine and corticosteroids may act via a metabolic effect. All other acute drugs act by reducing pain generation in the trigeminovascular system, the final common pathway that is responsible for the headache and associated symptoms of the migraine attack and can be ignited by the upstream lying metabolic disturbances."

Summary

Increasingly, researchers are beginning to look at migraine as a solution rather than a problem; that the symptoms of migraine are the result of the body's attempt to restore homeostasis following disruption of metabolic systems involving diet, sleep, exercise, and adaption to

changes in weather and temperature. This new knowledge can inform approaches to therapy that focus on preventing future attacks and improving results with abortive treatments.

References

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