An Introduction to Migraine, Its Biologic Origin and Its Treatment

The Whats, Hows and Whys of Migraine

What is "Migraine"?

Migraine. Upwards of 40 million Americans have it. Its annual cost to our economy amounts to tens of billions of dollars. It's the most common neurologic disorder encountered in outpatient clinics. And, like the weather, everyone talks about it… even makes jokes about it ("*not tonight, honey, etc.*"), but surprisingly few people - migraineurs themselves and medical providers included - really know much about migraine.

Ask anyone, a stranger, a friend or a neighbor who suffers from migraine: *What is "migraine"?*, and the answers you receive are likely to be both widely varied and largely inaccurate. Given the prevalence of migraine, the burden it imposes upon the public health and its cost to our economy, the fact that even most healthcare providers cannot define migraine – let alone treat it effectively – represents a real problem. A major "unmet need", as public health experts would term it.

What is migraine *not*? Migraine does not always involve a bad headache; some migraine episodes involve no headache at all, and others involve headache that is identical to the low intensity tension-type headaches that almost all of us experience at some time or another. While migraine is commonly aggravated by physical or emotional stress, migraine is not simply "psychosomatic"…a physical manifestation of an underlying psychological disorder. Migraine is not always a headache triggered by red wine, menses and chocolate; most often, migraine attacks occur without an identifiable trigger. Migraine does not always involve weird visual symptoms (flashing lights, zig-zags, blind spots) followed by a bad headache; only 20-25% of migraineurs ever experience aura.

What the term migraine *does* imply is that you, the migraineur, have experienced at least 5 episodes of spontaneously occurring headache that persisted for at least 4 hours (and for as long as 3 days), that prohibited or significantly inhibited your performing routine daily activities and that was accompanied by nausea and/or uncharacteristic sensitivity to light and noise. Sometimes the headache pain is severe. Sometimes not. Sometimes the pain may be throbbing. Sometimes not. Sometimes the pain may be lateralized to one side of the head. Sometimes not. Symptomatically, migraine is the Baskin-

Robbins of headache: migraine episodes come in a wide variety of flavors.

Do you have migraine?

Well, have you had…

5 or more attacks of head pain…

- *lasting 4-72 hours (untreated or unsuccessfully treated), with…*
- *at least 2 of the following characteristics:*
  1. *lateralized to one side of the head*
  2. *throbbing/pulsing/pounding*
  3. *moderate or severe intensity*
  4. *pain increased by routine physical activity, and…*
- *at least 1 of the following:*
  1. *nausea and/or vomiting*
  2. *sensitivity to both light and sound?*

If your answer is yes, and if other causes of headache that can mimic migraine have been excluded, then you have migraine.

This is the clinical definition of migraine.

> **Symptomatically, migraine is the Baskin-Robbins of headache…**

All well and good, but why is 12% of the general population prone to attacks of recurrent headache that at times may be functionally incapacitating? Biologically speaking, what *causes* migraine? That's where things start to get interesting.

What Causes Migraine?

Why do the 40 million Americans afflicted with migraine have this disorder in the first place? Biologically speaking, what differentiates a migraine person from a non-migraine person? Important questions. Without answers it obviously becomes difficult to develop therapies that can offer relief.

Most homes run on electricity, and a home's electrical system is organized into individual circuits. The same is true for the nervous system: it is genetically "wired" to contain many individual circuits. To put it simply, those who are said to have "migraine" possess a biologic circuit within the nervous system that is either absent in those free of migraine or present but typically silent unless provoked by a powerful stimulus (those of us who at times have overindulged in their intake of alcohol need only remember their last serious hangover).

In migraine, the biologic circuit is genetically sensitized to the point that it may activate in response to less raucous stimuli (egs, a single glass of wine; a drop in estrogen level at the onset of monthly menstrual flow; sleeping in on the weekend) or even spontaneously, with no identifiable stimulus whatsoever.

Like all circuits within the nervous system, the migraine circuitry is powered by *electro-chemical transmission* along a series of "wires" (axons, nerves) that microscopically resemble coaxial cables. When the migraine circuit is activated, an electronic head pain signal travels from one region of the nervous system to another. When the signal arrives at a way station, it causes a chemical to be released, and that chemical in turn induces a reaction that allows the electronic pain signal to continue on its way. Eventually the signal arrives at its final destination and causes the awaiting tissue to react in a manner that generates the headache and miserable accompanying symptoms of a migraine attack.

So what? Who cares? Well, if one desires to develop a therapy that potentially can "short-circuit" the migraine circuitry and terminate a migraine attack (acute therapy) or "rheostat down" the sensitivity of the circuit so that fewer attacks occur (prevention therapy), it helps to know what chemicals are the major players in the circuit's mechanism of electro-chemical transmission. In migraine, two key chemicals are protein molecules: serotonin and calcitonin gene related peptide (CGRP).

Develop a medication that can block the receptors to these proteins or can disable

the proteins, and the circuit will become "desensitized". Target certain serotonin receptors in the circuit that block the transmission of head pain signal and… *voila!* You have sumatriptan, a "designer drug" developed in the late 1980s that ignited a revolution in migraine therapeutics which has persisted up to the present time. Much more recently arrived are the anti-CGRP medications that - taken orally, received intravenously or self-administered subcutaneously – may effectively treat acute migraine, prevent migraine attacks, or both.

How Do You Treat Migraine?

In the end, to be effective any migraine treatment must be capable of desensitizing/stabilizing the biologic circuit which is producing the unwanted symptoms. If pharmacologic therapy is to be employed, the watershed choice in management lies between aggressive acute therapy only or a course of prevention therapy combined with acute therapy to treat such "break-through" attacks as may occur.

How do you make that choice? While professional headache organizations provide guidelines suggesting when prevention therapy should be considered, there really is no answer that suits the needs and preferences of all patients. Whichever approach is taken, acute therapy only versus prevention therapy + acute therapy, the treatment plan should be based on the patient's current "migraine burden". Accurate assessment of migraine burden is a surprisingly complex task [see *How Bad are Your Headaches?*], but the two key components typically are headache frequency and headache intensity.

If you have migraine and are experiencing headaches on a daily or near-daily basis, it is unlikely that even the most aggressive and effective acute therapy will be sufficient to adequately reduce your migraine burden. Most often you will need a course of prevention therapy to effectively stabilize your sensitized migraine circuit and so reduce the frequency and severity of your headaches.

On the other hand, if you are having 4 or 5 days of migrainous headache per month and have not yet tried pharmacological therapy specifically intended for acute migraine treatment, then the csae for prevention therapy may be much less compelling. There is accumulating evidence that aggressive and effective acute migraine treatment may assist not only in terminating acute migraine episodes as they occur; such treatment may also exert a "downstream" prevention effect and reduce headache frequency. If this is your situation, it is not an unreasonable choice to hold off on prevention therapy and see how things go with acute migraine treatment only.

Along with headache frequency and intensity, there are many other variables that must go into the blender before an appropriate pharmacologic treatment strategy can be chosen. What are the various pharmacologic options available? What are the potential side effects of the medications under consideration? If you are female and fertile, will you soon be attempting to conceive? if no, are you practicing adequate contraception? If a course of prevention therapy appears to be indicated, how do you feel about a

pill taken daily or every other day, versus subcutaneous self-injection once per month versus Botox injections every 12 weeks versus intravenous therapy every 3 months? For acute "rescue" from your most severe migraine headaches are you willing to self-inject a medication, or would you prefer a nasal spray? Much to consider. If you have questions or concerns, share them with your provider. No migraine therapy will be effective if you find yourself disinclined to use it.

If we have a clear understanding of migraine's biologic circuitry and now have available medications designed to fit that circuitry which have been meticulously evaluated and found to be safe, tolerable, and effective… why is there not a therapy that "works" for everyone with migraine? A good question. From clinical research trials, we know that even the best acute therapy for migraine is rarely effective in more than 70% of patients, and for migraine prevention medications that response rate generally hovers around 50%. There are many potential reasons why a given migraine therapy may not not effective in a sizable segment of the migraine population, but one that many find particularly compelling involves the acknowledgement that there is no single "migraine gene". Thus far we have identified well over 40 genetic permutations that each may yield the constellation of symptoms we name "migraine", and with such genetic variation – not to mention epigenetic factors (a topic best left for another day) – it stands to reason that there are accompanying variations in the biologic circuitry which may render that circuitry more or less susceptible to a given therapy. As we have virtually no means of identifying up-front what medication will work for what patient, despite the many advances of the last few decades migraine therapeutics remains a process of educated trial and error.

A last word. There are many ways to skin the migraine cat, therapeutically speaking. Designer drugs for acute migraine treatment or migraine prevention are great, but there are also non-pharmacologic methods for desensitizing the migraine circuit. Aerobic conditioning, good sleep hygiene, a healthy diet and avoidance of migraine "triggers" may for many migraineurs be just as effective as prevention medication…or, at least, serve with medication as a powerful co-therapy. Just as migraine is "much more than just a headache", successful management of migraine often requires more than just a pill.

> **"The migraine circuitry is powered by electro-chemical transmis-sion…**

The Biologic Circuitry of Migraine

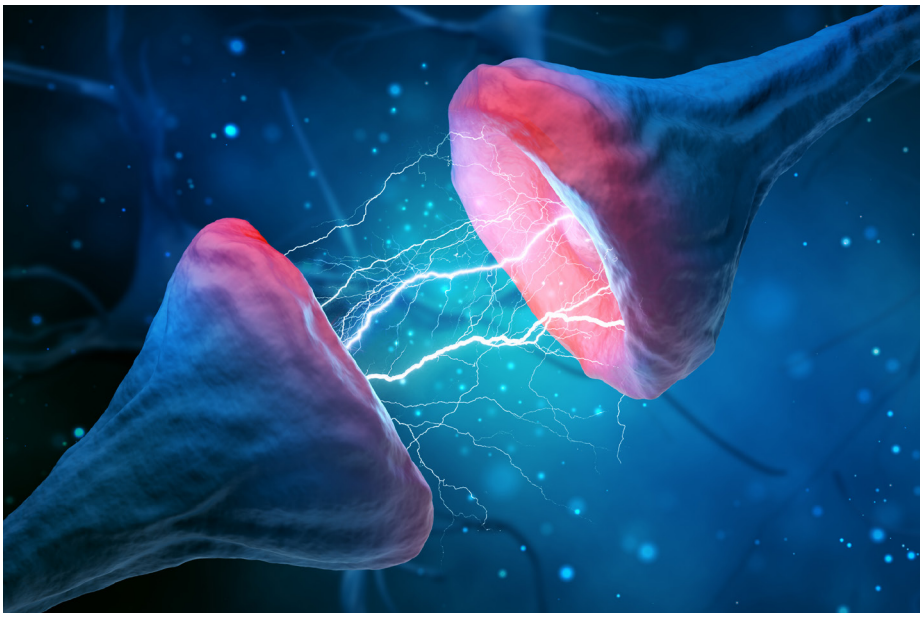
As mentioned in the What Causes Migraine? section, migraine is the product of a circuit powered by electro-chemical transmission. Serotonin and CGRP are the major chemical components of that circuit. What are its anatomical components?

To begin with, the brains of migraineurs are biologically different from those of non-migraineurs. Migraineur brains are "hypersensitive"; they do not tolerate well even minor degrees of head trauma, menses, a glass of red wine, infection with COVID or a host of other stimuli that would produce little or no problem with headache in a non-migraineur. That hypersensitivity is most prominent anatomically in and around the occipital lobes, that portion of the brain which receives visual input from the eyes, assembles that input, and enables us to perceive the environment around us.

In those individuals who experience visual aura, the aura symptoms most often result from excitation of brain cells (neurons) within the occipital cortex. While the precise headwaters of the migraine circuit have yet to be confirmed, many investigators feel that, as with aura symptoms, the headache of migraine originates as a consequence of abnormal electrical activity within the genetically sensitized neurons of the occipital lobe.

Downstream of the brain proper is the brainstem, that portion of the central nervous system which connects brain with spinal cord. Within the brain stem there is a long, skinny collection of neurons which is called the trigeminal nucleus caudalis (TNC). The TNC serves as a major waystation for the conduction of head pain signal, and within the TNC there are receptors to serotonin which may influence whether or not the head pain signal is passed along to more distal portions of the migraine circuitry. The triptans (eg, sumatriptan/Imitrex) are medications which activate certain serotonin receptors that block the passage of head pain signal. Initially it was assumed that the triptans exerted their therapeutic effect at a point further downstream in the circuitry, but many have come to believe they "short-circuit the circuit" by activating inhibitory serotonin receptors within the TNC.

> **...why is there not a therapy that "works" for everyone with migraine?**



The wire (axons) that connects the TNC with blood vessels in the outside lining of the brain (the dura, the outer-most layer of the meninges) is the trigeminal nerve. If a head pain signal is allowed passage by the TNC, it will make its way along the nerve to a dural blood vessel. At the junction between the nerve and blood vessel is a space, and into that space the nerve terminals release chemicals that bind with receptors on the vessel. One of the most important of those chemicals is calcitonin gene-related peptide (CGRP), and in this issue's "Migraine Treatments of the Month" we discuss the anti-CGRP monoclonal antibodies that were developed to prevent the linkage of CGRP with its receptors on the blood vessel...and thus prevent the migraine symptoms that occur when that linkage is made and the circuit is complete.

It is at this "trigeminovascular" junction that the physiological events which produce migraine headache appear to occur. When the chemicals released by the nerve terminals journey across the intervening space to bind with their receptors on the dural blood vessels, those vessels tend to dilate and to leak proteins that cause the area around the vessels to become inflamed. This inflammation within the meninges, this *meningitis*, accounts for why you may find that during an acute migraine headache episode your pain is increased by sudden head movements, bending over or coughing/sneezing. If there are dural arteries in the vicinity of the inflamed area, your pain may throb in synch with arterial pulsing. It also may account for why anti-inflammatory medication may be so effective for some patients in treating their acute migraine headaches.

So these are the primary anatomical components of the migraine circuit: occipital lobe, TNC, trigeminal nerve, trigeminovascular junction and dural blood vessels. Just like an interstate highway which has many on-ramps allowing entrance, it's likely that activation of any component of the circuit may lead the entire circuit to become acutely "sensitized" and so generate an acute migraine episode. That sensitization may be self-reinforcing, and migraine symptoms may intensify in parallel with increasing sensitization of the biologic circuit. In most cases, this acute sensitization eventually wears itself out and ceases spontaneously, is desensitized by sleep or responds to medication appropriate for acute migraine treatment. In some cases, however, the circuit remains chronically sensitized, and the unfortunate patient with chronic migraine is always either experiencing headache or on the brink of headache. In such cases it typically will require prevention therapy to effectively desensitize the circuit and reduce migraine burden.