The involvement of the immune system in chronic headache has been speculated upon since the 1970s. Various components of the immune system have been examined in relation to headache. While great strides have been made in advancing our understanding of neuroimmunology, the complexities of the system make its specific role in headache pathology unclear. This paper describes some of the key elements in the immune system and their relation to headache pathogenesis.

Calcitonin Gene-related Peptide (CGRP)
CGRP in an inflammatory neuropeptide involved at every level of migraine pathophysiology, including the meninges, trigeminal ganglion, trigeminocervical complex, brainstem nuclei, thalamus, and the cortex. Upon initiation of migraine at the brainstem or cortex level, neurogenic inflammation occurs such that peripheral trigeminocervical neurons are activated. We then observe a release of CGRP and other neuroinflammatory peptides. CGRP induces neurogenic vasodilation that leads to further plasma protein extravasation and the influx of mast cells and other pro-inflammatory cells. The process of neurogenic inflammation sensitizes the peripheral nociceptors transmitting via the trigeminal axon, through the brainstem and the thalamus, and finally into the cortex.

In animal models, CGRP is released following stimulation of the central nervous system (CNS)—similar to what is observed in migraine. Triptans inhibit the animal’s CGRP release. In humans, injections of CGRP into migraine patients result in delayed headache. Certain studies have suggested that relief of migraine corresponds to a reduction of CGRP levels in the blood and that migraine-specific therapy with triptans decreases CGRP. These studies have led to the development of CGRP-receptor antagonists that could conceivably block neurogenic vasodilation in the meninges. CGRP activity in the trigeminal ganglion may limit vasoconstriction.

Two CGRP-receptor antagonists, olcegepant and telcagepant, have been tested in phase II trials and are currently in phase III trials. This new class of agents holds great promise for migraine-specific treatment without the troublesome vasoconstrictive effects of triptans.

Cytokines
Recent studies have revealed that the neuropeptide CGRP triggers the secretion of cytokines via stimulation of CGRP receptors found on T-cells. Cytokines are involved in inflammation, in modulation of the pain threshold and also in trigeminal nerve fiber sensitization. In small trials, cytokines have been proven to precipitate headache.

In trials where tumor necrosis factor (TNF) was injected, headaches were shown to be induced while, on the other hand, the TNF antibody was shown to reduce pain in humans. Plasma levels of both pro- and anti-inflammatory cytokines are enhanced during migraine attacks. TNF levels increase after migraine pain onset and decrease progressively over time after the onset of the attack. Plasma levels of a pro-inflammatory cytokine, IL-1, are also enhanced after the initiation of headache. IL-1 release is induced by TNF and may lead to hyperalgesia. The amount of an anti-inflammatory cytokine, IL-10, has also been shown to increase after the onset of a headache and may be involved in analgesia. One study revealed IL-10 inhibited release of TNF, which is anti-nociceptive.

Cytokine levels in the cerebrospinal fluid (CSF) of migraineurs have been studied with varied results. Increases in IL-1 receptor antagonist (IL-1ra), monocyte chemoattractant protein-1 (MCP-
1) and transforming growth factor-1 (TGF-1) were measured in patients with migraine and episodic tension-type headache (TTH) versus pain-free controls. Rather than being the cause of headache, changes in the level of cytokines in the CSF are thought to be due to pain.11 No correlation has linked increased cytokine levels to a decrease in pain and there has not been a difference found in cytokine levels with migraine versus episodic TTH.13

**Tumor Necrosis Factor**

TNF is a pro-inflammatory cytokine involved in inflammation and it is crucial in the activation of pain. A small number of patients with new daily persistent headache (NDPH) develop symptoms after viral infection. It is possible that a pro-inflammatory cytokine such as TNF could initiate and maintain CNS inflammation even after the infection resolves. Rozen et al12 reported elevated levels of cerebrospinal fluid TNF in 19 of 20 NDPH patients, in 16 of 16 chronic migraine patients, and in 2 of 2 chronic tension headache patients. The study suggests that TNF plays a role in the etiology of these types of headache. Refractory chronic daily headache could involve increased levels of CSF TNF. Patients with NDPH (and, theoretically, elevated TNF) often are refractory to a variety of medication regimens.

TNF is important in a number of conditions such as sinusitis and rhinitis, as well as headache.15 Development of drugs that modulate TNF may prove beneficial to these conditions as well as headache.

**Adiponectin**

Obesity is known to be a major risk factor for the development of chronic migraine.18 Adipose tissue secretes adipocytokine adiponectin, which is believed to modulate several inflammatory mediators important in migraine. A large amount of adipose tissue leads to decreased secretion of adiponectin.19 Adiponectin has a protective role in limiting the development of insulin resistance, dyslipidemia and atherosclerosis. It also has an anti-inflammatory action through inhibition of cytokines IL-6 and TNF-induced IL-8 production. Adiponectin induces the production of cytokine IL-10, which is anti-inflammatory. Adiponectin decreases migraine but, paradoxically, a sudden increase may worsen a headache.18

**Glia and Headache**

Recent studies have shown that glial cells, previously thought to serve only a supportive role, are now known to directly influence the microenvironment of trigeminal ganglion neurons through gap junctions and paracrine signaling.20 Following trigeminal activation, CGRP secreted from neuronal cell bodies activates adjacent glial cells to release nitric oxide (NO) and inflammatory cytokines which, in turn, initiate inflammatory events in the trigeminal ganglia that lead to peripheral sensitization.21,22 The neuronal glial-signaling is thought to be an important process, ultimately leading to the initiation of migraine. The glial modulation of neurons through immune mediators is an unexplored area for new migraine medications. An excellent report on glia research by Drs. Moskovitz and Cooper appeared in these pages in the November/December 2010 issue.23

**Mast Cells**

It is generally accepted that migraines are partially mediated by prolonged activation of meningeal nociceptors (pain receptors). One possible explanation of how this occurs seems to be found in the physiology of mast cells. Mast cells are granulated immune cells that play a critical role in inflammation. They have been found to reside in high density in the intercranial dura, a peripheral tissue covering the brain.24 Mast cells are located in close proximity to the blood vessels and the primary afferent nociceptive neurons.

When the mast cells are stimulated, they degranulate their contents into the local milieu. This activates the surrounding trigeminal meningeal nociceptors and promotes a prolonged state of excitation. It is not clear if there is a specific molecule released from the mast cells that is responsible for the propagation of migraine. Several of the degranulated molecules have implications for migraine. The list includes histamine, leukotrienes, the cytokines TNF and IL-6, and endothelin-1.25,26

Once the meningeal nociceptors are activated by the release of mast cell molecules, they propagate a cascade of neuronal activation by releasing neuropeptides (e.g., CGRP, substance P). These activate and further degranulate residual mast cells and thus prolong the migraine headache. According to Levy, et al,27 the key lies in the increased expression of the phosphorylated form of the extracellular signal-related kinase (pERK). This is an anatomical marker for nociceptor activation and downstream signaling of the spinal trigeminal nucleus.

**Seasonal Allergies and Headache**

The association between seasonal allergies and headaches has been well-documented in several studies.28-32 A recent study found that headaches are 1.5 times more common in those with atopic conditions (asthma, seasonal allergic rhino-sinusitis, chronic bronchitis) than those without these disorders.28

“A recent study found that headaches are 1.5 times more common in those with atopic conditions (asthma, seasonal allergic rhino-sinusitis, chronic bronchitis) than those without these disorders.”28

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examination is crucial since appropriate treatment highly depends upon a proper diagnosis.

Many patients who believe they have sinus headaches are suffering from migraine. In fact, sinus headache is the most common misdiagnosis of patients with migraine. For its part, the International Headache Society (IHS) does not recognize sinus headache as a diagnostic entity—unless it is associated with a confirmed diagnosis of underlying acute rhino-sinusitis.

Conclusion

The immune system plays a key role in migraine pathogenesis. The involvement of CGRP is important in neurogenic vasodilation, peripheral sensitization, and the initiation of the migraine cascade. Various cytokines, including TNF, IL-1, and adiponectin, have been implicated in the precipitation of migraine.

The role of allergies in migraine remains a confusing area. In headache-prone individuals, seasonal allergies may be a trigger and most people diagnosed with sinus headaches are actually suffering from migraine.

The earliest work on the immune system and headache focused on mast cells and their role in propagating the cascade of neuronal activation when degranulated. The supporting glia cells, long thought to be inert, have been found to modulate neuronal activity—partly through immune mediators. The manipulation of immune system elements is a promising area of development for new headache therapies, although these may be many years in development.

Lawrence Robbins, MD, was awarded the 2008 Janet Travell clinical pain management award by the American Academy of Pain Management. He has been chosen as one of “America’s Top Doctors” every year since 2002. He has certificates in pain management and psychopharmacology. He has published two headache books—one for patients (Robbins L. and Lang S., Headache Help, 2nd edition, Houghton Mifflin, 2000) and one for physicians (Robbins L., Management of Headache and Headache Medications, 2nd edition, Springer Verlag, 2000)—and 175 articles and abstracts. He has served his patients in his Northbrook, IL, headache clinic since 1986. The Dr. Robbins Show is available on headachedrugs.com and talkzone.com. Dr. Robbins is also an Assistant Professor of Neurology at Rush Medical College. He can be contacted at 1535 Lake Cook Road, Northbrook, IL 60062; phone 847-480-9399; fax 847-480-9044.

References