Migraine rats, medical facts

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Migraine mechanisms are still far from being fully understood. Escalating data from animal models are "fact-checking" the neurophysiological and behavioral correlates of the migraine experience in humans. A series of studies published in the journal *Cephalalgia*, the official journal of the International Headache Society, have described the underlying mechanisms and molecules related to migraine, and how they may be affected by current anti-migraine drugs or might translate into new therapies.

Evidence suggests that migraine can originate from either central or peripheral mechanisms. Central mechanisms mean that changes in structures of the central nervous system, such as the cortex, hypothalamus, thalamus, among others, are altered, modifying brain excitability, leading to headache attacks. One mechanism believed to cause migraine is cortical spreading depression (CSD). CSD is a depolarization wave of the neurons that spreads from the occipital cortex (neck region) to the parietal cortex and is also related to the migraine aura. The peripheral mechanism, on the other hand, involves the activation of nociceptors (neurons that process painful stimuli) in the meninges that surround the brain and cerebral vessels. However, CSD (with central origin) can activate the trigeminovascular system, where the nociceptors of the meninges and brain vessels originate. In a series of recent studies, these animal models are shedding more light on migraine therapies and etiological mechanisms.

Onabotulinum toxin A

Onabotulinum toxin type A (Botox) has been shown to be effective in the treatment of chronic migraine. Studies carried out with lab animals simulating neurophysiological mechanisms of the disease, are beginning to reveal how these medications work against migraine.

A research group from the Beth Israel Deaconess Medical Center and Harvard Medical School, led by Dr. Rami Burstein, showed that the induction of CSD in rats, simulating a migraine attack, activates the trigeminovascular system and increases the triggering of nociceptors from the meninges. More recently, this same group of researchers showed that in female rats the application of Botox applied peripherally to the lambdoid and sagittal sutures reduced the nociceptor shots induced by CSD by 72%, indicating that the activation of nociceptors by central migraine-inducing phenomena, such as CSD, can be blocked by Botox.

CGRP

The calcitonin gene-related peptide (CGRP)) is an inflammatory and vasodilator neuropeptide that is elevated in the circulation of people with migraine and induces migraine in these patients when injected intravenously.

A growing number of studies in preclinical migraine models have shown that females are more susceptible to the nociceptive effects of CGRP, possibly due to estrogen amplifying effects on CGRP receptors. A Brazilian study, led by Dr. Juliana Geremias Chichorro, from the Federal University of Paraná, showed in another animal model of migraine that the CGRP applied within the trigeminal ganglion was able to induce neurophysiological and behavioral responses in male and female rats similar to migraine in humans, such as cutaneous allodynia (when the scalp/skin becomes painful to non-painful stimuli), intolerance to light (photophobia) and anxiety behavior. Interestingly, drugs with neuroprotective actions such as minocycline and propentophylline were

effective in inhibiting the effects of CGRP only in male rats. However, sumatriptan, which is currently prescribed to abort migraine attacks, was effective in inhibiting the action of CGRP in both sexes.

PACAP-38

Last but not least, research from Dr. Lars Edvinsson's lab at the University of Lund, Sweden, found that in rats, another migraine-related emerging neuropeptide, namely, the pituitary adenylate cyclase-activating polypeptide (PACAP-38), co-localized with CGRP in areas of the brain that are related to the origin of migraine attacks. PACAP-38 and CGRP matched well in the cerebral cortex, cerebellum, thalamus, hypothalamus, the pons and spinal trigeminal nucleus, which are well-known neuroanatomic sites related to migraine.

These are a few examples of how pre-clinical studies go further into migraine mechanisms of symptoms and behaviors in humans, as well as provide insightful data on migraine therapies' mechanisms of action.

More information: Karin Warfvinge et al, Cellular distribution of PACAP-38 and PACAP receptors in the rat brain: Relation to migraine activated regions, *Cephalalgia* (2019). DOI: 10.1177/0333102419893962

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