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PACAP38, a Migraine Attack Inducer, Suggests New Treatment Target

Pituitary adenylate cyclase-activating polypeptide-38 induces headache in healthy subjects and migraine-like attacks in migraineurs.

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OJAI, CA—Infusion of the neuropeptide pituitary adenylate cyclase-activating polypeptide-38 (PACAP38) induces headache and vasodilatation in healthy subjects and migraineurs. Among migraineurs, PACAP38 infusion also may induce migraine-like attacks that are associated with sustained dilatation of extracranial arteries and elevated plasma PACAP38 before attack onset. Taken together, research indicates that PACAP38 is involved in migraine pathophysiology and may have implications for migraine therapy, according to a presentation at the 11th Annual Headache Cooperative of the Pacific Winter Conference.

Investigators at the University of Copenhagen's Danish Headache Center, including Jes Olesen, MD, Professor of Neurology, have studied PACAP38. Dr. Olesen compared their work on PACAP38 to their prior studies of calcitonin gene-related peptide (CGRP), which contributed to the development of a new class of migraine drugs known as selective CGRP antagonists.

"What got the industry around to producing and testing a drug were our studies with the human model where we infused CGRP and placebo in a crossover study and demonstrated that CGRP infusion can cause a migraine attack," Dr. Olesen said. Although it makes sense that blocking a peptide that induces migraine may lead to effective treatment, "it is not invariably so," he said. "With CGRP, it is wonderful that it actually proved to be right, and so now we have the drugs against CGRP and its receptors."

Jes Olesen, MD

Similar Peptides With Different Effects

PACAP38 is structurally and functionally related to vasoactive intestinal polypeptide (VIP), but their effects on headache differ. Rahmann et al in 2008 studied 12 patients with migraine without aura who received infusions of VIP. None of the subjects reported a migraine attack after VIP infusion. The few instances of headache were mild. The investigators concluded that VIP does not trigger migraine attacks in migraineurs.

Similar studies of PACAP38, however, found that infusion of PACAP38 does induce headache and migraine-like attacks. Schytz et al in 2009 reported that PACAP38 infusion caused headache in all healthy subjects (n = 12) and in 11 of 12 patients with migraine, seven of whom experienced migraine-like attacks. None of the participants had headache after receiving placebo. Half of the migraineurs reported that onset of migraine-like attacks occurred several hours (mean, six hours) after the start of the PACAP38 infusions. "It's a long-lasting effect, and there is a tendency for most of the headaches to come pretty late," Dr. Olesen said.

With such observations in mind, Amin et al in 2014 undertook a head-to-head comparison of PACAP38 and VIP in a double-blind crossover study of female patients with migraine without aura. Patients were randomly allocated to IV infusion of PACAP38 or VIP over 20 minutes. Patients then received the other infusion at least one week later. Of the 22 patients who completed the study (mean age, 24), 16 patients (73%) reported migraine-like attacks after PACAP38 infusion, whereas four patients (18%) reported migraine-like attacks after VIP infusion. Three of the four patients who reported migraine-like attacks after VIP infusion also reported migraine-like attacks after PACAP38 infusion. Some of the migraine attacks could have been spontaneous and unrelated to the infusions, Dr. Olesen noted. Nevertheless, "it is clear that highly significantly more patients got a migraine attack with PACAP than with VIP," Dr. Olesen said.

Is the PAC_1 Receptor Key?

Further insights into PACAP38 have emerged from animal studies, one of which involves the potentially important role of the PAC_1 receptor in migraine. PACAP38 works on the three most prominent receptors in the cerebral vasculature: PAC_1, $VPAC_1$, and $VPAC_2$. VIP, by contrast, works on $VPAC_1$ and $VPAC_2$, but not on PAC_1. The two compounds have the same affinity to $VPAC_1$ and $VPAC_2$. "So, isn't it almost obvious that since PACAP causes a migraine attack and VIP does not, it must be via the PAC_1 receptor?" Dr. Olesen asked. "Well, we think so, but how can we be sure? That is the logic of the data until somebody comes up with something else."

A study led by Dr. Olesen's colleague and wife, Inger Jansen-Olesen, DMSc, suggests another difference between VIP and PACAP38 that may be relevant to migraine. Dr. Jansen-Olesen and colleagues compared the effect of PACAP38 and VIP on CGRP release in the trigeminal nucleus caudalis in rats. Increasing doses of PACAP38 increased release of CGRP, whereas increasing doses of

VIP did not. “VIP does not liberate CGRP. That is at least one difference between PACAP and VIP that may be relevant,” Dr. Olesen said.

Whether the PAC_1 receptor is responsible for migraine induction is the “million-dollar question,” Dr. Olesen said. Several companies, based on their experience with CGRP, have the ability to develop human antibodies against PACAP38 or any of its three receptors relatively quickly, he said. “We would put our money on an antibody that blocks the PAC_1 receptor because you like a drug to be as specific as possible,” said Dr. Olesen. “We do not want to block three receptors if we only have to block one receptor.”The same philosophy applies to blocking the PACAP38 molecule itself. “You ... take away the signals to all three kinds of receptors, so it is likely that you would have more side effects,” Dr. Olesen said. On the other hand, whether migraine induction involves the PAC_1 receptor or other mechanisms remains unclear. “I think [studies] will show in the not-too-distant future whether antibodies against the PAC_1 receptor will be effective in migraine,” said Dr. Olesen.

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Jes Olesen, MD

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