BRAINSTEM CGRP AND CGRP RECEPTOR EXPRESSION

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Migraine is a chronic and disabling brain disorder that affects up to 15% of the population. The disorder is typically one-sided, often throbbing head pain, and is associated with nausea, photophobia and phonophobia. The underlying mechanisms have been debated for a very long time and much suggests that is has its origin in the CNS; however, a key component is the pain-producing sensory innervation of the trigeminovascular system. This system includes the trigeminal ganglion (ophthalmic part), the dura mater with the meningeal artery and the large cerebral arteries of the circle of Willis, and the nerve cell's afferent projections to the brainstem trigeminal nucleus caudalis (TNC) and reciprocal regions at the C1-C2 levels of the spinal cord. The sensory cranial vascular projections are strictly one-sided, with the exception of the proximal part of the circle of Willis and the superior sagittal sinus (SSS). Calcitonin gene-related peptide (CGRP) is the most abundantly expressed of the neuronal messengers in this system. The projections from the cranial vasculature to the brainstem show a somatotopic organization with sensory unmyelinated C-fibers storing CGRP and mechanosensitive myelinated Aδ-fibers with CGRP receptor elements.

Few tracing studies have been performed using local administration of a tracer into regions such as the lamina I/II or deeper. Collectively the experiments carried out so far show direct connections to brainstem regions periaqueductal grey (PAG) and the ventral posterior lamina (VPL) of the thalamus.

Several studies have shown release of CGRP in migraine attacks, correlating with the pain and that triptan administration aborts both the pain and the CGRP increase. In addition, CGRP receptor antagonists show antimigraine effects in clinical studies, however, it is debated if their action is mediated via peripheral and/or central sites. There is growing evidence in support that brainstem nuclei can modulate the trigeminocervical complex responses to a peripheral stimulation of the SSS.

We have recently examined in some detail the localization of CGRP and CGRP receptors (CLR and RAMP1) in rat and human brainstem in order to provide a morphological basis for a central site of CGRP receptor mechanisms in headache disorders. The C-fibers store CGRP and the Aδ-fibers store CLR and RAMP1 in the spinal cord lamina I/II; these fibers have before been shown to originate in the trigeminal ganglion. The findings support the possibility that they may interact locally and are not co-stored. Thus, there are several sites both peripherally and centrally that exhibit CGRP receptor expression and these could putatively be involved in the antimigraine responses to gepants.