

NESTIN/HRAMP1 Transgenic Mice: A Novel Migraine Model

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Objectives: To study light aversive behavior and trigeminal mediated pain as surrogates of photophobia and head pain in nestin/hRAMP1 mice.

Background: While the initial triggering of migraine attacks remains unknown, it is widely accepted that trigeminovascular system activation and the neuropeptide calcitonin gene-related peptide (CGRP) play a key role in the pathophysiology of migraine. As previously reported, we have generated a transgenic mouse that is sensitized to CGRP by overexpression of the human receptor activity modifying protein 1 (hRAMP1) subunit of the CGRP receptor in the nervous system (nestin/hRAMP1 mouse).

Methods: nestin/hRAMP1 mice were tested in the light aversion test before and after intracerebroventricular (icv) administration of CGRP. The light aversion test is a natural conflict based assay. Mice were tested individually in a chamber with two compartments, half-enclosed and dark and half-open and lit, joined by a small opening in the center. Total time spent in the light was measured. Olcegepant was coadministered icv with CGRP. Rizatriptan and sumatriptan were administered subcutaneously with CGRP icv. For the trigeminal mediated pain studies, a novel operant assay was used where mice are given a choice between a reward and avoidance of painful thermal stimulus in the face.

Results: Untreated nestin/hRAMP1 transgenic mice spent 30% less time in the light than their littermates ($P < 0.0001$). CGRP icv caused around 80% decrease in the time spent in the light ($P < 0.001$). CGRP-induced light aversion was prevented by olcegepant, rizatriptan, and sumatriptan. Studies analyzing motor activity, anxiety related behavior and morphology of the anterior segment of the eye of nestin/hRAMP1 and control mice revealed that none of these can fully explain the light aversive behavior displayed by nestin/hRAMP1 mice. Trigeminal mediated nociception is not increased in untreated nestin/hRAMP1 mice at different noxious temperatures. Ongoing studies to address the effect of CGRP and nitroglycerine in trigeminal mediated nociception will be reported.

Conclusions: These results indicate that *RAMP1* gene transfer can increase CGRP actions in the nervous system. Nestin/hRAMP1 transgenic mice are more light aversive than littermates and this is greatly enhanced by icv administration of CGRP. This behavior can be objectively quantified and used as a surrogate of the photophobia. The replication of the CGRP-induced light aversive behavior in a different pedigree confirmed the contribution of nestin-cre driven hRAMP1 expression to the phenotype

independent of the genetic context. The reproduction of the same results in a different testing chamber corroborates the robust phenotype. The effect of olcegepant, rizatriptan, and sumatriptan abolishing the CGRP-induced light aversion validate the usefulness of this model for future mechanistic studies and drug development.

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