

## ALTERATIONS IN NEUROGENIC INFLAMMATORY RESPONSES IN MICE LACKING $\alpha$ CGRP

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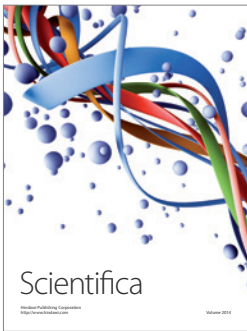
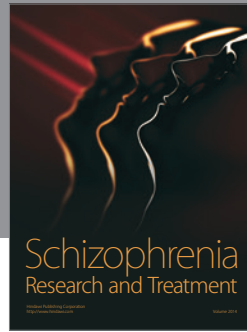
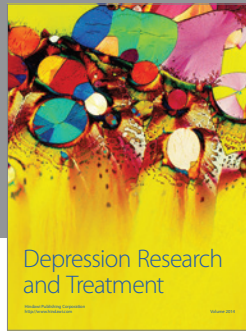
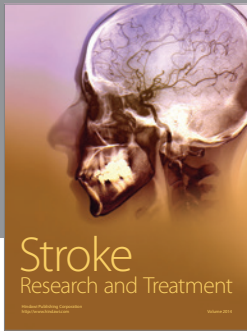
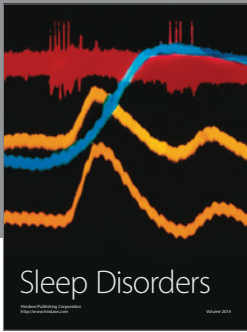
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$\alpha$ -Calcitonin gene-related peptide ( $\alpha$ CGRP) is a pleiotropic peptide neuromodulator that is widely expressed throughout the central and peripheral nervous systems. Although CGRP has been implicated in numerous physiological processes (including peripheral vasodilatation, acetylcholine receptor biosynthesis, nociception, and neurogenic inflammation), the precise physiological roles of CGRP remain to be elucidated. To provide a better understanding of the physiological role(s) mediated by this peptide neurotransmitter, we have generated  $\alpha$ CGRP-null mice by targeted modification in embryonic stem cells.

Numerous studies have indicated that the release of CGRP and tachykinins from the peripheral endings of sensory nerves leads to a neurogenic inflammatory response characterized by an edematous reaction resulting from local vasodilatation and plasma extravasation. Topical administration of capsaicin (8-methyl-N-vanillyl-6-noneamide) to the ears of wild-type mice resulted in a rapid increase in ear thickness ( $0.12 \pm 0.03$  mm), yet the response of heterozygous ( $0.10 \pm 0.01$  mm) and homozygous  $\alpha$ CGRP-null animals ( $0.06 \pm 0.01$  mm) was significantly diminished. Direct assessment of plasma extravasation in capsaicin-treated animals, using intravenous administration of Evans Blue, paralleled the results observed with changes in ear thickness ( $\Delta T$ ) as plasma extravasation was reduced in  $\alpha$ CGRP-null mice by 56% when compared to control animals. The observed decreases in neurogenic inflammatory response were comparable to those seen for mice lacking expression of the preprotachykinin A (PPT-A) gene. Similar decreases in both ear edema and plasma extravasation were observed for  $\alpha$ CGRP-null animals upon topical administration of mustard oil (allyl isothiocyanate), suggesting that both capsaicin and mustard oil were acting through similar mechanisms. To further examine the relationship between capsaicin- and mustard oil-mediated neurogenic inflammation, animals were pretreated with either capsaicin or mustard oil, followed by a second application of one of these irritants after 20 h. Initial application of either capsaicin or mustard oil resulted in a robust increase in ear thickness ( $0.12 \pm 0.02$  mm and  $0.09 \pm 0.02$  mm, respectively), whereas the  $\Delta T$  was significantly diminished after a second application of the same compound. Topical application of capsaicin or mustard oil, followed by subsequent administration of the alternate compound, also resulted in a decreased  $\Delta T$  suggesting a heterologous desensitization of this inflammatory response.

In addition to tachykinins and CGRP, arachidonic acid metabolites have also been shown to be important mediators in several models of acute inflammation. Topical application of arachidonic acid resulted in a similar edematous response for both wild-type and  $\alpha$ CGRP-null animals, suggesting that the pathways linking arachidonic acid to acute inflammation were unaffected in  $\alpha$ CGRP-null mice. Pretreatment of wild-type and mutant animals with the nonspecific cyclooxygenase inhibitor, indomethacin, significantly decreased capsaicin- and arachidonate-mediated edema formation for both animal genotypes suggesting that arachidonic

acid metabolites not only play a critical role in capsaicin-mediated neurogenic inflammation, but also that such metabolites are downstream of CGRP release from sensory afferent fibers.



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