

## **ROLE OF ESTROGENS IN THE MODULATION OF INFLAMMATORY PAIN: A STUDY IN AROMATASE KNOCK-OUT MICE USING THE TRIGEMINAL FORMALIN MODEL.**

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Sex-related differences in pain perception are known in humans and animals. Gonadal hormones, in particular estrogens, have been identified as the major determinant of this sexual dimorphism. In the present study, we investigated the influence of gender and of estrogens on inflammatory pain using the orofacial formalin test in mice. We measured the frequency of rubbing of the formalin-injected lip in male and female estrogen-deficient aromatase knock-out (ArKO, Cyp 19) mice and in their wild type littermates (WT). Two supplementary groups of male and female ArKO mice received a 7-day  $\beta$ -estradiol treatment (5 $\mu$ g, s.c.) before the formalin test.

There was no difference in nociceptive behaviour between male and female WT mice neither in the first acute phase of pain nor in the second "tonic" phase. By contrast, lip rubbing was significantly more pronounced in ArKO than in WT females during the second phase. ArKO males did not differ significantly from their WT littermates regarding phases 1 and 2, but, contrary to the latter, they displayed a third phase of pain behaviour 36 minutes after the formalin injection. In ArKO mice treated with  $\beta$ -estradiol the differences in second phase for females and third phase for males were not detectable anymore.

Taken together, these results confirm the role of estrogens in inflammatory pain modulation. The increased nociceptive behaviour in ArKO mice and its reversal by  $\beta$ -estradiol indicate that this hormone has globally an antinociceptive effect and that the different behaviour in ArKO mice is not due to developmental changes. The differences between male and female ArKO mice suggest, however, that the mechanisms of nociceptive modulation by estrogens or of pain processing itself differs between genders.

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