Chronic treatment with fluoxetine induces sex-dependent analgesic effects and modulates HDAC2 and mGlu2 expression in female mice.

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In recent years gender and sex differences in pain recognition and drug responses have been extensively investigated both in clinical trials and experimental models of pain. Antidepressant drugs are largely used in the treatment of different forms of chronic pain. While it is generally accepted that the tricyclic antidepressant (TCA), amitriptyline, and the serotonin/noreprinephine reuptake inhibitor (SNRI), duloxetine, are effective in persistent pain (1,2), there is less agreement about the efficacy of antidepressants belonging to the selective serotonin reuptake inhibitor (SSRI) class, including fluoxetine (3-5).

In experimental models of pain antidepressant drugs are usually evaluated after acute administration and we have previously shown that fluoxetine is also effective in the formalin test after a single intraperitoneal injection and that the analgesic activity is lost in mice lacking central serotonergic neurons (6). However protocols of acute treatment do not reproduce the clinical use of these drugs.

In this study we evaluated sex differences in the analgesic effects of fluoxetine after chronic administration (10 mg/kg, ip, for 21 days) in male and female CD1 mice in the formalin test, a model of persistent inflammatory pain. Moreover, since antidepressant treatment may induce direct epigenetic effects and fluoxetine itself is known to modulate the expression of epigenetic modifying enzymes (7), we measured changes in histone deacetylase 2 (HDAC2) and metabotropic glutamate type 2 (mGlu2) expression in dorsal root ganglia (DRG) and dorsal horn.

We here show that chronic treatment with fluoxetine reduces the second phase of the formalin test only in female mice without producing behavioral changes in males.

We also observed that chronic treatment with fluoxetine reduces the expression of HDAC2 in DRG and dorsal horns of female mice together with an of increases histone 3 acetylation level. These effects nicely correlate with an increased expression of mGlu2 receptors in the dorsal horn of the spinal cord exclusively in female mice. Interestingly, we have previously shown that epigenetic mechanisms that up-regulate mGlu2 expression in the dorsal horn of the spinal cord are strictly related to analgesic effect in rodents (8-12).

With this study we provide evidence that antidepressant drugs might have sex-specific analgesic effects after chronic administration. The observation that fluoxetine induces sex specific changes in HDAC2 and mGlu2 expression in the dorsal horn of the spinal cord and in DRGs provides a molecular explanation for the analgesic effects in female mice and suggests that estrogens and/or estrogen receptors might play a role in the observed effects.

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