Gender-specific effects of long-term fluoxetine treatment in the mouse formalin test

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Antidepressant drugs are commonly used in various chronic pain syndromes. While there is a general consensus that the tricyclic antidepressant (TCA), amitriptyline, is the gold standard of analgesic antidepressants, analgesia obtained with selective serotonin reuptake inhibitors (SSRI) is less consistent.
Long-term treatment with antidepressant drugs is known to increase hippocampal brain-derived neurotrophic factor (BDNF) and this effect is thought to underlie the effectiveness of these drugs in depression. However, BDNF is also considered a central modulator in the development of pain sensitization.
Also, a number of studies point to a gender distinct effect of BDNF on depression-like behavior in rats, suggesting that there may be a sexual dimorphism in BDNF function. Moreover, a sex-differentiated pharmacokinetic profile has been reported for antidepressant drugs.
Based on this evidence, in this work we sought to evaluate the effect of long-term treatment of fluoxetine on pain behavior and on BDNF expression in the spinal cord of male and female mice. Pain behavior was evaluated after a 21-day treatment with fluoxetine (20 mg/kg p.o) in adult male and female CD1 mice in the hot plate and formalin test.
Consistent with data from literature, our study demonstrate that chronically injected fluoxetine fails to induce analgesia in both tests in male mice. However, in female mice, fluoxetine treatment induced a significant reduction in the second phase of the formalin test but not in the hot plate, suggesting the involvement of mechanisms underlying the development of central sensitization. Consistent with this hypothesis, the analgesic effect of fluoxetine in female mice correlated with a reduction in BDNF expression in the lumbar segment of the spinal cord.
Our results show a gender-specific effects of fluoxetine on pain behavior. It is known that fluoxetine is metabolized faster in females than in males with a higher production of the metabolite norfluoxetine. Thus, pharmacokinetics differences might underlie this gender-specific effect.