Gender specific effects of Antidepressant drugs in pain behavior and spinal BDNF expression in mice

M. Zammataro[1,2], M. Barresi[1], S. Merlo[2], M.A. Sortino[2], S. Chiechio[1]

[1]Dept. of Drug Sciences, University of Catania, Italy
[2]Dept. of Biomedical and Biotechnological Sciences, University of Catania, Italy

Among antidepressant drugs the tricyclic (TCA), amitriptyline, is considered the gold standard of analgesic antidepressants, for the treatment of different chronic pain syndromes. Moreover, the dual serotonin/norepinephrine inhibitor (SNRI), duloxetine, has been shown to be efficacious both in persistent and inflammatory pain states. On the contrary, analgesia obtained with selective serotonin reuptake inhibitors (SSRI) is less consistent.
Although the serotonergic and noradrenergic systems have been implicated in the descending inhibitory control of pain and therefore in the analgesic effects of antidepressant drugs, in this study we evaluate whether brain-derived neurotrophic factor (BDNF) might also be involved.
While increase in hippocampal BDNF, is considered the underlying mechanism supporting the effectiveness of these drugs in depression, spinal BDNF is also considered a central modulator in the development of pain sensitization.

Furthermore, 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.

Based on this evidence, in this work we sought to evaluate the effect of long-term treatment of different classes of antidepressants on pain behavior and on BDNF expression in the spinal cord of male and female mice. We selected fluoxetine, amitriptyline and duloxetine as representative for SSRI, TCA, and SNRI classes of antidepressant drugs, respectively. Pain behavior and BDNF expression in the dorsal horn of the spinal cord were evaluated after a 21-day treatment (10 mg/kg, ip) with the three antidepressants both in male and female CD1 mice.

Our results show a gender differentiated behavior in the formalin test of male and female littermate mice after a long-term administration of antidepressants. Specifically, a 21-day treatment with fluoxetine was unable to elicit analgesic response in both phases of the formalin test in male mice, but was able to significantly reduce the second phase of the formalin test in females. On the contrary, duloxetine and amitriptyline did not affect nocifensive behavior in the formalin test, in female mice, but they induced analgesia in males. Moreover, western blotting and immunohistochemistry analyses show that antidepressant drugs can differently modulate BDNF expression in the dorsal horn of male and female CD1 mice, suggesting that BDNF participates to pain modulation by antidepressant drugs in a gender specific manner.