Role of central histaminergic system in the analgesic and antidepressant-like effects induced by endogenous PPAR-alpha ligands in mice

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Several reports demonstrated that the treatment with endogenous agonists of the nuclear peroxisome proliferator-activated receptor alpha (PPARα), oleoylethanolamide (OEA) and palmitoylethanolamide (PEA) induced anti-inflammatory, anti-hyperalgesic and antidepressant-like effects in rodents. We recently demonstrate that neuronal histamine contributes to OEA-induced hypophagic effect. As evidence indicates that brain histamine is involved in the pathophysiology of depression and pain transmission, here we investigated if PPARα-induced analgesic and and antidepressant-like effects requires the integrity of the central histaminergic system. To this aim we evaluated the effects of OEA and PEA treatment in mice unable to synthesize histamine (histidine decarboxylase knock-out, HDC-KO) and normal littermates (wild type, WT) in classical models predictive of antidepressant-like and antinociceptive activities: the tail suspension test (TST) and the acetic acid-induced abdominal writhing test, respectively. Animals were treated with vehicle, OEA (5 and 10 mg/kg, i.p.), PEA (2.5, 5 and 10 mg/kg, i.p.) or imipramine (10 mg/kg, i.p.) using two different regimen: sub-chronic (24, 5 and 1 hour before test) and chronic (once daily for 7 days) before challenge in the TST. Treatment with OEA at both doses and PEA at highest dose induced a dose-dependent reduction of immobility time when compared with vehicle-treated animals with both sub-chronic and chronic regimen. These effects were not observed in mice lacking neuronal histamine, since no differences were observed among groups. In another set of experiments, WT and HDC-KO mice received an acetic acid (0.8%, ip) injection 30 min after OEA (5 and 10 mg/kg, ip) or vehicle acute treatment. Writhings frequency was reduced in OEA-treated WT mice as compared with control, but the effect did not reach statistical significance. Taken together, these data suggest that the histaminergic system contributes to PPARα-induced analgesic and antidepressant-like effects, and indicate that PPARa may be an attractive target for the development of innovative antidepressant and analgesic drugs.