THE FAT SENSING MOLECULE OLEOYLETHANOLAMIDE INDUCES ANTIDEPRESSANT-RELATED RESPONSES BY TARGETING PPAR-α AND RECRUITING THE HISTAMINERGIC NEUROTRANSMISSION.

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Oleoylethanolamide (OEA) is a gut-derived fat sensing molecule and preclinical studies demonstrated its antidepressant-like activity in animal models (Jin et al., 2015). Previous data indicate that the hypophagic effects of OEA are mediated at least in part by PPAR-α (Fu et al., 2003), albeit other receptors may also be implicated in OEA's action. Here we investigated if the antidepressant-like effect of OEA as well is mediated by PPAR-α and whether the central histaminergic system is involved in this effect. We previously observed that neuronal histamine (HA) participates to OEA-induced central effects (Provensi et al., 2014). Thus, we investigated if brain HA is also required for OEA-induced antidepressant-like effect. Both behavioral and neurochemical tests were used. PPAR-α-knockout and wild type (WT) mice were subjected to repeated (3x in 24hrs) or sub-chronic (1/die x 8 days) treatment with OEA (10mg/kg, i.p.) or vehicle and challenged in the Tail Suspension Test (TST). In the same animals, cortical and hippocampal CREB phosphorylation was measured by Western Blot analysis. Repeated and sub-chronic OEA treatment induced a significant reduction in the immobility time of WT mice indicative of anti-depressant like efficacy. In PPAR-α-KO mice no differences were observed between OEA and VEH treated animals. In keeping with this observation, OEA-induced increase in cortical and hippocampal CREB phosphorylation was impaired in PPAR-α-KO animals. Mice unable to synthesize histamine due to either disruption of the histidine decarboxylase gene (HDC-KO) or alpha-fluoromethylhistidine (an inhibitor of this enzyme, 5µg/5µL, i.c.v.) injection and WT littermates were treated with repeated or subchronic OEA (5 or 10 mg/kg), imipramine (10 mg/kg) or vehicle i.p. administrations and tested in the TST. OEA significantly reduced the immobility time of WT and control mice, but this effect was not observed in HA deficient mice. Imipramine reduced immobility time of HA-deprived mice as well. Results of cortical and hippocampal pCREB paralleled the behavioral data. In conclusion, OEA antidepressant-like effect is mediated by PPAR-α activation and this effect depends on the integrity of the brain histaminergic system.

Jin et al. (2015). Pharmacol Biochem Behav. 133:146-54

Fu et al. (2003). Nature. 425:90-3.

Provensi et al. (2014). Proc Natl Acad Sci. 111:11527-32