Peroxisome proliferator-activated receptor (PPAR)-alpha activation produces antidepressant-like effects in mice

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Peroxisome proliferators-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor superfamily (Kliewer et al., 1994; Forman et al., 1996). PPAR-alpha, one of the three isoforms to date known, controls anti-inflammatory programs of transcription (Delerive et al., 2001; Kostadinova et al., 2005). However, behavioral effects resulting from PPAR-alpha pharmacological activation are still largely unknown. Considering that depressive symptoms constitute a comorbidity of several inflammatory conditions (Ghia et al., 2009), we aimed to test a possible anti-depressant-like effect of PPAR-alpha agonists.

Male ICR mice were subjected to the forced swim test (FST), whereas male wild-type and PPAR-alpha -/- C57BL6 mice were used for tail suspension test (TST). The synthetic PPAR-alpha agonists GW7647 [2-(4-(2-(1-cyclohexanebutyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid], Wy-14,643 [4-chloro-6-(2,3-xylidino)-2-pyrimidinylthioacetic acid] and the endogenous PPAR-alpha agonist, PEA (palmitoylethanolamide), were administered by intraperitoneal (ip) route (10-50 mg kg^{-1}) 30 or 180 minutes before test session. Locomotor effects were evaluated in the open field test (OFT) while anxiety-related behaviors were evaluated in the elevated plus maze test (EPM). For brain-restricted drug administration mice were implanted with an intracerebroventricular (icv) cannula system.

PPAR-alpha synthetic agonists reduced immobility time in FST and TST in mice. At dose used no locomotor alterations and anxiety-like responses were observed. Wy-14,643 failed to induce antidepressant-like effects in PPAR-alpha-null mice.

Antidepressant-like effect was rapid and centrally mediated, since it was magnified when PPAR-alpha agonists were directly delivered to the brain.

These data add further support to a broad range of pharmacological properties underlying PPAR-alpha activation (D'Agostino et al., 2012). The anti-depressant-like properties of its agonists reinforce the role of PPAR-alpha as a promising anti-inflammatory target with a likely positive effect on depression that often characterizes chronic inflammatory states.

References:

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