Neuronal PPARγ modulates anxiety-like behaviour in mice

E. Domi[1], L. Soverchia[1], S.Uhrig[2], A.C. Hansson[2], R. Spanagel[1], R. Ciccocioppo[1], M. Ubaldi[1]

[1]School of Pharmacy, Pharmacology Unit, University of Camerino, Camerino 62032, Italy
[2]Institute of Psychopharmacology at the Central Institute of Mental Health, Medical Faculty Mannheim/University of Heidelberg, 68159, Germany

Stress is considered to be a key causal factor in depression and anxiety behaviour (Rolak et al., 2007). Recent preclinical and clinical studies report antidepressant effects following activation of PPARγ by the synthetic agonist pioglitazone (Sadaghiani et al., 2011;Kemp et al., 2014; Zeinoddini et al., 2015).
To better understand the role of PPARγ in the modulation of these behaviours we set out a series of experiments: using neuron-specific PPARγ knock-out (PPARγ KO) and wild type counterpart (Wt) mice to test the effect of the selective PPARγ agonist pioglitazone and the antagonist GW9662. Specifically, we tested anxiety behavior in the elevated plus maze (EPM), open field (OF) and light dark (LD) test at basal conditions and after restraint stress. Moreover we performed a c-Fos analysis on PPARγ KO and Wt mice to identify the brain regions activated after a mild stress caused by the exposure to the LD box. To confirm neuronal lack of PPARγ gene in KO mice we carried out an in situ hybridization analysis (ISH) of PPARγ transcripts in selected brain areas. To monitor the hypothalamic-pituitary axis (HPA) function we assessed glucocorticoids levels in PPARγ KO and Wt under basal conditions and following stress. Finally, guided by the neuronal activity changes we performed microinjections of pioglitazone (5mg/μl) in the amygdala of the Wt mice and assessed anxiety behaviour in the LD test in basal conditions and after restraint stress.
The results demonstrated that PPARγ KO mice showed higher levels of basal anxiety compared to their Wt counterpart in all three test carried out (EPM, LD and OF). Pioglitazone (30 mg/kg) reversed the anxiogenic effect induced by the acute restraint stress while PPARγ antagonist GW9662 (5mg/kg) induced an anxiogenic behaviour in the Wt mice but not in the PPARγ KO mice. Following exposure to LD apparatus c-Fos analysis showed a different neuronal activation between PPARγ KO and Wt in limbic areas including the amygdala. No differences were observed in regions related to stress hormonal response such as paraventricular nucleus of the hypothalamus (PVN) and paraventricular area (PVA). Consistently, in Wt and KO animals corticosterone levels showed the same basal level and pattern of activation following stress. Finally, pioglitazone microinjections reduced anxiety induced by stress revealing an important role of the amygdala in mediating PPARγ's effects.
Altogether these findings provide strong evidence for the role of PPARγ in anxiety indicating that activation of the receptors might result in anxiolytic action via modulation of emotion-related areas.

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