The PPARα agonist clofibrate reverts the cognitive impairment induced by the sub-chronic treatment with phencyclidine

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Schizophrenia is a severe neuropsychiatric disorder affecting approximately 1% of the population worldwide and is characterized by three major groups of symptoms, positive symptoms, negative symptoms and cognitive deficits (Andreansen, 1995; Rössler et al., 2005). Antipsychotic medications are mainly used in the treatment of schizophrenia but a considerable number of patients do not respond satisfactorily to the treatment and there are a significant number of side effects associated with their use (Hasan et al., 2012). Peroxisome proliferator activated receptors alpha (PPAR-α) are nuclear receptors transcription factors involved in different physiological functions (Pistis and Melis, 2010). They are activated by endogenous ligands like fatty acid amides N-palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) as well as by synthetic ligands such as the hypolipidemic drug fibrates. PPAR-α are widely expressed in different brain areas involved in schizophrenia like the mesolimbic dopamine system and cortical areas such as the prefrontal cortex (Moreno et al., 2004). A gene association study indicated a possible role of PPAR-α receptors in the susceptibility of schizophrenia (Costa et al., 2013), and two clinical studies reported variation of PEA levels in cerebrospinal fluid and blood of schizophrenic patients (Giuffrida et al., 2004; Leweke et al., 1999) suggesting an involvement of these receptors and their ligands in this psychiatric disorder. To date, no study evaluated so far a possible antipsychotic profile of PPAR-α agonists. The present study was designed to evaluate the prospective antipsychotic effect of the synthetic PPAR-α agonist clofibrate in a pharmacological animal model of schizophrenia. In adult Sprague Dawley rats it has been showed that an acute administration of the non-competitive N-methyl-D-aspartate receptor antagonist phencyclidine (PCP 5 mg/kg intraperitoneally) was able to induce positive-like symptoms of schizophrenia such as hyperactivity, stereotypies and impaired sensorimotor gating in the prepulse inhibition (PPI) test of the acoustic startle reflex (Cascio et al., 2015). Using this model, we found that an acute injection of clofibrate, at dose that by itself does not affect spontaneous locomotor activity (25 mg/kg), was unable to revert hyperlocomotion, stereotypies and impaired PPI induced by the acute injection of PCP. However, when we used the sub-chronic treatment of PCP (5 mg/kg i.p. twice day for 7 consecutive days) that induced cognitive deficits in the novel object recognition (NOR) test (Redrobe et al., 2012), acute clofibrate (25 mg/kg i.p.) that by itself does not affect recognition memory in NOR paradigm, was able to significantly attenuate the cognitive deficits. In preclinical research, catalepsy is an animal behavior widely used to evaluate the antipsychotic-induced extrapyramidal symptoms in humans. Compared to haloperidol, clofibrate did not induce catalepsy in the bar test at any dose tested (100, 250 and 500 mg/kg i.p.). In conclusion, these data show that the synthetic PPAR-α agonist clofibrate may be useful for the treatment of cognitive dysfunctions in schizophrenia, without having undesirable central nervous system side effects.