

# **CLOZAPINE-LIKE PROFILE OF THE CANNABINOID RECEPTOR ANTAGONIST SR141716A ON RODENT MODELS OF DEFICIENT SENSORIMOTOR GATING**

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Schizophrenia is a disease involving deficits in one or more of the multiple mechanisms that enable normal individuals to filter or “gate” most of the sensory stimuli they receive. As a group such mechanisms are referred to as sensorimotor gating. Prepulse inhibition (PPI) of the startle reflex provides an operational measure of this and can be assessed across species using similar stimuli to elicit comparable response characteristics. The phenomenon of PPI occurs when brief non- startling acoustic, visual or tactile stimuli are presented 20- 500 ms before the startling stimulus. PPI is known to be significantly reduced in schizophrenic patients and in rodents after one of the following pharmacological manipulations: stimulation of D2 dopamine receptors, using apomorphine or amphetamine; activation of serotonergic systems, by means of serotonin releasers or direct receptor agonists; blockade of NMDA receptors, using non- competitive antagonists such as phencyclidine (PCP), dizocilpine (MK-801) or ketamine. Disruption of PPI induced by NMDA-receptors antagonists has been used as an animal model of positive and negative symptoms of schizophrenia and previous studies indicate that atypical, but not typical, neuroleptics can selectively restore PPI in this model.

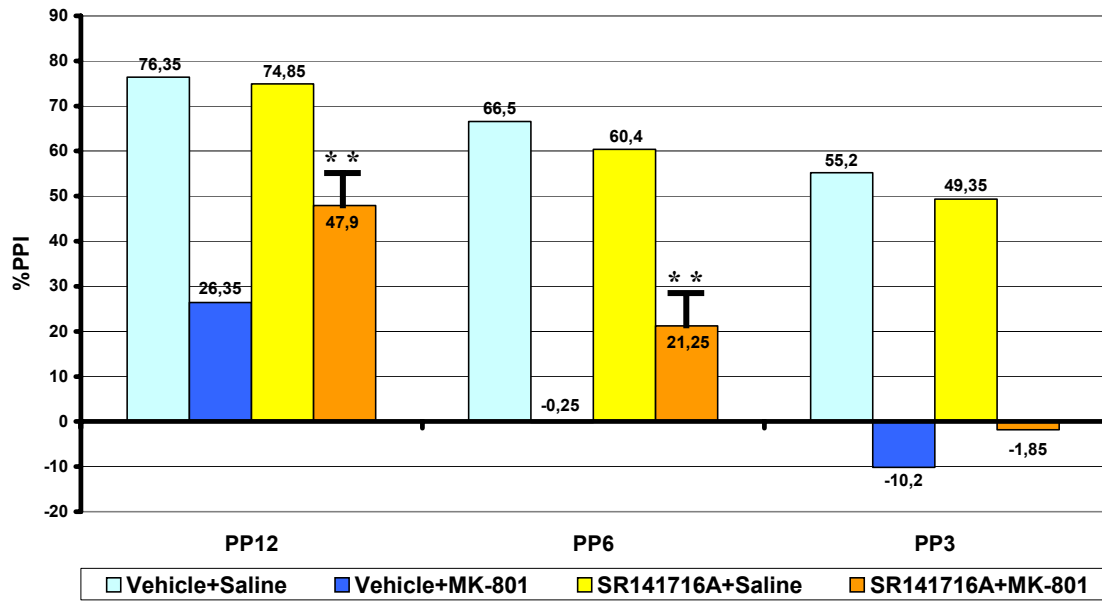
Cannabinoids are known to have psychotropic effects in humans and clinical signs of chronic cannabis consumption may also resemble negative symptoms of schizophrenic disorders. The resulting suggestion that the etiology of schizophrenia may include an imbalance in endogenous cannabinoid signalling has led to the cannabinoid hypothesis of schizophrenia.

On the bases of both this hypothesis and previous studies, showing that cannabinoids seem to act as dopaminergic and glutamatergic systems modulators, we have studied the effects of the cannabinoid CB1 receptors antagonist SR141716A on NMDA- antagonists- induced disruption of PPI. SR141716A was analyzed in 3 PPI paradigms: PCP- and MK-801- induced disruption of PPI, which have been shown to be preferentially reversed by antipsychotics, and apomorphine- induced disruption of PPI. From the analysis of the results of these experiments it appeared that SR141716A is able to significantly reverse both PCP- and MK-801- induced deficits in PPI while it has no effects on apomorphine- induced disruption.

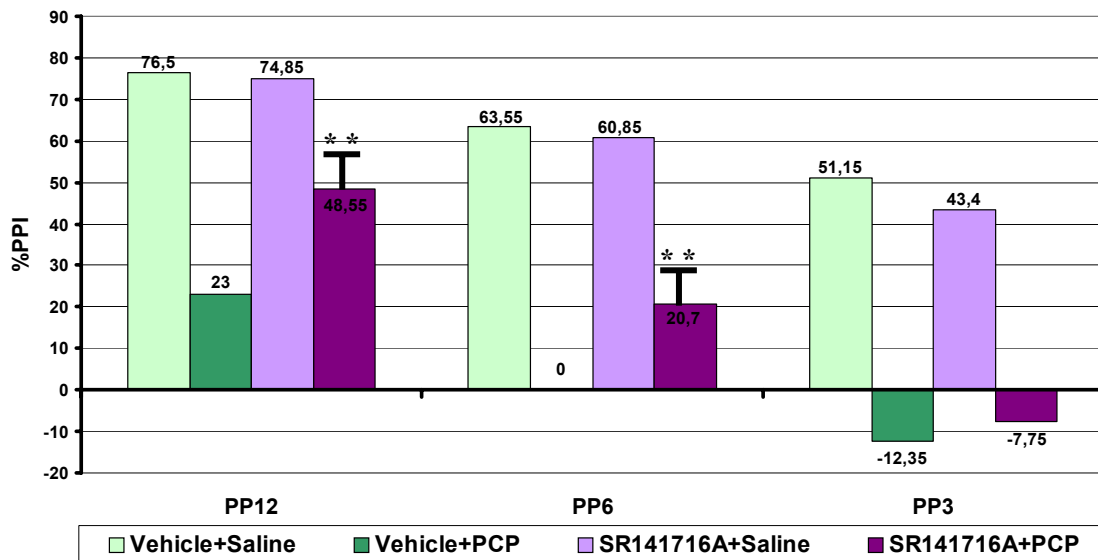
Our data indicate that SR141716A is functionally similar to atypical antipsychotics, showing a clozapine-like profile that makes this substance a good candidate for further studies assessing its therapeutic potential in the treatment of schizophrenic patients. Our conclusion is also supported by preliminar experiments conducted in our laboratory and by previous findings that the blockade of cannabinoid CB1 receptors by SR141716A increases Fos- and neurotensin- like immunoreactivity with characteristics comparable to those reported for atypical antipsychotics such as clozapine.

## **List of most relevant papers related with the topics**

- Emrich HM, Leweke FM, Schneider U. (1997) Towards a cannabinoid hypothesis of schizophrenia: cognitive impairments due to dysregulation of the endogenous cannabinoid system. *Pharmacol Biochem Behav*: 56(4):803-807
- Mansbach RS, Geyer MA. (1989) Effects of phencyclidine and phencyclidine biologs on sensorimotor gating in the rat. *Neuropsychopharmacology*: 2:299-308
- Rinaldi-Cremona M, Barth F, Héaulme M, Shire D, Calandra B, Congy C, Martinez S, Maruani J, Néliat G, Caput D, Farrara P, Soubrié P, Brelière JC, Le Fur G. (1994) SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Letters*: 350:240-244



**Effects of MK-801 and SR141716A on PPI:** rats were treated with vehicle (1 ml/kg s.c.) + saline (1 ml/kg s.c.), vehicle (1 ml/kg s.c.) + MK-801 (0,1 mg/kg s.c.), SR141716A (1,5 mg/kg s.c.) + saline (1 ml/kg s.c.) and SR141716A (1,5 mg/kg s.c.) + MK-801 (0,1 mg/kg s.c.) \*\* =  $p < 0,001$  Vs. MK-



**Effects of PCP and SR141716A on PPI:** rats were treated with vehicle (1 ml/kg s.c.) + saline (1 ml/kg s.c.), vehicle (1 ml/kg s.c.) + PCP (1 mg/kg s.c.), SR141716A (1,5 mg/kg s.c.) + saline (1 ml/kg s.c.) and SR141716A (1,5 mg/kg s.c.) + PCP (0.1 mg/kg s.c.) \*\* =  $n < 0,001$  Vs. PCP