ROLE OF CB1 RECEPTOR SYSTEM IN A PHARMACOLOGICAL MODELS OF SCHIZOPHRENIA

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Clinical and laboratory findings suggest that cannabinoid signalling is implicated in schizophrenia, however the interaction remains poorly understood, as data are often contradictory. On the basis of the intriguing but still confusing results present in literature, the aim of the present study is to investigate the role of the CB1 receptor system and signalling in a pharmacological model of schizophrenia.

The pharmacological model is based on repeated injections of the non-competitive NMDA antagonist, phencyclidine (PCP, 2,5 mg/kg, chronic intermittent treatment for 1 month). This is a validated model that mirrors the metabolic hypofunction and some of the neurochemical abnormalities observed in schizophrenia, such as a decrease of parvalbumin mRNA expression, that reflect a down-regulation of expression due to decreased activity of GABAergic interneurons. 72 hours after the last PCP injection, brains have been analyzed for CB1 receptor binding and CP-55,940-stimulated $[^{35}S]GTP\gamma S$ binding. Our results show that CB1 receptor levels are not modified by the pharmacological treatment but significant alterations in the coupling to G proteins are found in specific cerebral areas such as prefrontal cortex (-23%), globus pallidus (+71%), hippocampus (-34%) and substantia nigra (-28%), areas involved in the control of motor, emotional and cognitive states.

On the animals exposed to subchronic PCP, we then performed behavioural tests such as locomotor activity, object recognition and sucrose preference. PCP treated rats showed increased stereotyped behavior, whereas any alterations in locomotor activity and sucrose preference were observed. Moreover, PCP treated animals showed an impairment in the object recognition test, a popular protocol to study learning and memory, suggesting the presence of altered cognitive function, a typical sign of schizophrenia. When PCP rats were co-treated with a low dose of THC (0.5 mg/kg, daily for three weeks) that per se was not able to induce any significant alterations in memory parameters, a worsening in cognitive parameters was found. Co-treated animals showed an CB1 receptor functionality that only partially overlapped the picture produced by PCP alone.

Taken together, our findings suggest that altered cannabinoid signalling is present in animal models of schizophrenia. Whether this alteration is produced by schizophrenia or able per se to favour schizophrenic-like symptoms is still a matter of speculation.