Understanding the role of dopamine D4 receptor regulation of mesolimbic dopamine function in a rat model of schizophrenia

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Abstract

The project concentrated on characterising the effect of D4 receptor activation in the context of an animal model relevant to schizophrenia (phencyclidine pretreatment) and elucidating the mechanisms involved. Behavioural studies measured selective attention to motivational stimuli, through measurement of latent inhibition of conditioned learning (LI), and episodic memory measured by novel object recognition (NOR), behaviours which are dysfunctional in schizophrenia. Subchronic PCP pre-treatment for five days disrupted LI and induced behavioural deficits in NOR, replicating previous findings using seven days pre-treatment. A412997 reversed deficit in NOR but not in LI. However, the neural the mechanisms these processes are as yet unclear.

A better understanding of the physiology of cortical-limbic circuits is important in elucidating the neurophysiological mechanisms underlying dopamine-mediated processes which are vital for normal behaviour, and which may be abnormal in schizophrenia. The project examined the neuropharmacology underlying these behavioural processes, both in normal animals, and in animals pretreated with phencyclidine. Focusing on the role of D4 receptors. To achieve these aims fast-scan cyclic voltammetry was used to measure electrically stimulated dopamine release in nucleus accumbens, in rat brain slices *in vitro*. The selective dopamine receptor agonist A412997 caused a decrease in electrically stimulated dopamine release which was abolished in animals pretreated with PCP. This inhibitory effect of A412997 was blocked by D4 specific antagonist L-741,742.

Gene expression of dopamine D4 receptors, as well as in other dopamine receptors (D1, D2, D3, D5) in response to sub-chronically pre-treated with PCP was significantly changed in different regions of rat brain, as well as these pre-treatment as modelling relevant to schizophrenia produced changes on the basal level of dopamine and its metabolites in the same brain areas.