Pramipexole disrupts synaptic plasticity in the CA1 area of the hippocampus of rats that develop contrafreeloading for water, an animal model of compulsive behavior

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Chronic treatment with the preferring D3 agonist pramipexole (PPX) elicits contrafreeloading (CFL), consisting in a compulsive selection of a suboptimal choice. Functional correlates of this behavior have never been investigated. As ventral hippocampus has been implicated in behavioral flexibility and decision-making, we tested whether the development of PPX-induced CFL is associated with an impairment of synaptic plasticity in this area.

Rats were trained under a fixed ratio 3 (FR3) schedule of reinforcement for water. On days 1-6, water was only available through lever pressing while from day 7 to 20 choice between contingent and non-contingent access was allowed. PPX 0.5 mg/kg or saline were administered intraperitoneally before the beginning of the session. Hippocampal slices from the same animals were used to study synaptic plasticity using extracellular recordings. Golgi-Cox staining was used to determine spine density on CA1 pyramidal neurons. Hippocampal synaptosomes were prepared and analyzed by immunoblotting.

PPX-treated rats exhibited a rigid behavior as they continued to work for water even though it was also non-contingently available, thus enhancing CFL. Moreover, only a fraction of water gained was actually consumed by PPX treated rats. LTP elicited by a single high-frequency stimulation train was reduced in PPX treated rats with respect to controls. PPX treatment was associated with a significant decrease of total spine density and PSD-95 expression with respect to saline treated group. In turn the activation of presynaptic proteins STX1a and SYN is enhanced. Interestingly JNK phosphorylation at synaptic level was increased.

We demonstrated that enhancement of CFL by PPX was associated with impairment of synaptic plasticity in the CA1 area of the hippocampus. As CFL results from a loss of behavioral flexibility and goal orientation, which represent the hallmarks of compulsive behaviors, we suggest that synaptic dysfunction in this area is relevant for the pathogenesis of compulsive symptoms caused by D3-preferring dopaminergic agents