Involvement of type 1 cannabinoid receptors in the modulation of dopamine output associated with food restriction in the rat prefrontal cortex

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Increase of dopamine output on corticolimbic structures, including the medial prefrontal cortex (mPFC) and nucleus accumbens, has been related to reward effects associated with palatable food or food presentation after a fasting period in rats. Increase in dopamine levels with the high levels of endogenous cannabinoids (eCBs) detected in limbic areas of food-restricted animals suggest that the eCB system might have an important role in the regulation of dopamine output in mFPC of FR rats. The neural actions of eCBs are mainly mediated through activation of the CB type 1 (CB1) receptors. Because of the predominant localization at presynaptic level in different brain areas such as the PFC, their activation leads to a decrease in the release of a variety of neurotransmitters, including GABA. To elucidate the contribution of CB1 receptors in the mechanism underlying the regulation of dopamine output in the mPFC associated with feeding, we employed the model of prolonged food restriction (FR) in Sprague-Dawley rats which consisted of limiting the food availability to a 2-h period daily for 3 weeks. In microdialysis experiments, FR rats showed a marked increase in the extracellular dopamine concentration in the mPFC starting 80 min before food presentation, with the concentration peaking during food consumption and returning to baseline after food removal. The changes were markedly attenuated by the administration of the CB1 receptor antagonist SR141716, but were unaffected by the agonist WIN 55, 212. In vitro electrophysiological experiments showed that basal $GABA_A$ receptor-mediated sIPSC frequency was significantly reduced in mPFC neurons of FR rats compared with control animals, an effect that may involve an altered function of presynaptic CB1, GABAB and D2 receptors, all present at mPFC inhibitory synapses. The reduced GABA release was accompanied by an enhanced excitability of mPFC glutamatergic as well as VTA dopaminergic neurons observed in FR rats. The reduction of sIPSC frequency induced by WIN 55,212 as well as the effect of DSI (Depolarization-induced Suppression of Inhibition) being markedly diminished in FR rats during the anticipatory phase before food presentation, suggest a reduction of CB1 receptor function. This effects were paralleled by a reduction of CB1 receptors expression observed in FR rats compared with controls. Interestingly we observed an increase of both presynaptic D2 and GABAB receptor function at mPFC GABAergic synapses. Moreover, a single injection of SR141716 in FR rats 1 h before food consumption was able to antagonize the FR-induced effects on the modifications of CB1 receptors function. Together, our data support the contribution of CB1 receptors in the regulation of dopamine output in the mPFC through changes in GABA inhibitory synapses and, in particular, suggest that changes in the activity and expression of CB1 receptors might be crucial triggering the alterations observed in the function of GABAergic synapses of FR rats and, in turn, on mPFC dopamine output.