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# Activation of type-1 cannabinoid receptor shifts the balance between excitation and inhibition towards excitation in layer II/III pyramidal neurons of the rat prelimbic cortex.

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## Abstract

Activation of the endocannabinoid (eCB) system by exogenous cannabinoids (drug abuse) can alter the physiology of the brain circuits involved in higher-order cognitive functions such as the medial prefrontal cortex (mPFC). A proper balance between excitation and inhibition (E/I balance) is critical for neuronal network oscillations underlying cognitive functions. Since type-1 cannabinoid receptors ($CB_1$Rs), expressed in many brain areas including the mPFC, can modulate excitatory and inhibitory neurotransmission, we aimed to determine whether $CB_1$R activation results in modifications of the E/I balance. We first confirm the presence of functional presynaptic $CB_1$Rs that can modulate both excitatory and inhibitory inputs to layer II/III pyramidal neurons of the prelimbic (PL) area of the mPFC. By decomposing the synaptic response evoked by layer I stimulation into its excitatory and inhibitory components, we show that in vitro $CB_1$R activation with the cannabinoid receptor agonists WIN55,212-2 (WIN) and CP-55940 (CP) modulates the balance between excitation and inhibition (E/I balance) of layer II/III pyramidal neurons. This treatment caused a significant shift of the E/I balance towards excitation, from 18/82 % to 25/75 % (WIN) and from 17/83 to 30/70 % (CP). Finally, when animals were injected with a cannabinoid receptor agonist, we observed a shift of the E/I balance (measured in vitro) towards excitation 1 h after WIN (24/76 %) or after CP injection (30/70 %) when compared to vehicle-injected animals (18/82 %). This modulation of the E/I balance by $CB_1$Rs may thus be fundamental in the regulation of local PL cortical network excitability and could be the mechanism through which excessive $CB_1$R activation (cannabis abuse) affects cognitive functions.

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