

Retrograde synaptic plasticity and metaplasticity induced by addictive drugs in the nucleus accumbens and the prefrontal cortex.

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Endocannabinoids (eCBs) belong to a newly described family of lipid neurotransmitter produced on demand in response to neuronal activity. In the central nervous system, eCBs act, via their activation of cannabinoid CB1 receptors (CB1R), as retrograde messengers to modulate synaptic transmission: at excitatory and inhibitory synapses of the central nervous system, eCBs produced by post-synaptic neurons in response to postsynaptic depolarization or intense synaptic activity, travel across the flow of synaptic transmission to induce either short or long-term depression of synaptic release. Our data demonstrate that in response to physiologically relevant stimuli, retrograde eCB signalling is involved in the long-term depression of glutamatergic excitatory transmission in the nucleus accumbens and the prefrontal cortex, two key structures involved decision making, motor planning and reward. We have studied the role of eCB-signalling in the tonic and phasic regulation of synaptic transmission in these two structures. Both single and repeated exposure to addictive drugs can alter synaptic plasticity in the brain reward pathway, this type of plasticity of plasticity ("metaplasticity") has been proposed to participate to the protracted changes in brain functions induced by addictive drugs. Despite its widespread use, the effects of cannabis derivatives on synaptic transmission and plasticity remain poorly understood. We found that single and repeated *in-vivo* exposure to a phytocannabinoid,  $\Delta^9$ -Tetrahydrocannabinol (THC, the principal psychoactive ingredient of cannabis) in the nucleus accumbens (NAc), can indeed induce the plasticity of plasticity in the brain reward pathway.