SYNAPTIC PLASTICITY IN COCAINE ADDICTION

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ABSTRACT

Addiction has been described as a pathological usurpation of the neuronal mechanisms involved in reward, motivation and reinforcement. Nevertheless, environmental stimuli closely associated with the drug can acquire the ability to elicit the emotional responses that were induced by the drug. From this perspective, addiction has something to do with long-term associative learning and memory. These effects induced by cocaine consumption account for the chronic relapse which characterizes addiction. Long-term potentiation (LTP) and long-term depression (LTD) are forms of synaptic plasticity by which chronic cocaine induces changes in the mesocorticolimbic system primarily through dopamine and glutamate transmission. Recent evidence suggests that brain-derived neurotrophic factor (BDNF) and its intracellular pathways are involved in the molecular mechanisms that modify synaptic plasticity underlying addiction.

A single dose of cocaine induces an enhancement in locomotor activity that correlates with an increase in synaptic strength (the ratio AMPAR/NMDAR) in the ventral tagmental area (VTA). This effect was not increased after repeated cocaine doses, indicating that cocaine-induced synaptic plasticity in the VTA is transient and also has a ceiling effect. Adaptations in downstream circuitry, such the nucleus accumbens (NAc), are likely to be more important for the longer-lasting behavioral changes associated with drug addiction. EPSC is decreased (LTD was induced) at synapses made by prefrontal cortical afferents in spiny neurons of the NAc shell, but not in the core. This inhibitory effect appears to be induced by D1 receptor activation. These changes in synaptic plasticity disrupt goal-directed behavior. In the dorsal striatum, LTP can be induced in physiological conditions as well as after chronic cocaine treatment. However, saline treated rats are able to reverse LTP, whereas cocaine treated rodents do not. In the dorsal striatum, LTP is induced by D1 receptor activation and enhanced by D2 receptor antagonists. In physiological conditions, the ability to reverse LTP at striatal synapses functions as a mechanism for "forgetting" maladaptive habits, thus the lack of ability to reverse LTP may have important consequences in drug addiction. Increased BDNF levels in VTA neurons during withdrawal from cocaine plays a role in synaptic remodeling. BDNF also promotes long-lasting changes in the mesolimbic dopamine system by activating mechanisms of associative learning that underlie persistent addictive behavior.