Role of intra-accumbens brain-derived neurotrophic factor on cue-induced reinstatement after cocaine self-administration

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Brain-derived neurotrophic factor (BDNF) has been shown to have a critical role not only on neurite growth during early stages of development, but also on physiological and pathological functions in the adult brain. Several studies have explored the role of BDNF in addiction-related brain regions, like prefrontal cortex, ventral tegmental area or shell and core (NAcore) of the nucleus accumbens. In adults, the expression of BDNF in the NAcore is low, and the two main sources of BDNF are glutamatergic projections from the PFC and dopaminergic input from the VTA. Both D1- and D2-receptor-expressing medium spiny neurons (MSNs) of the NAcore express the primary receptor for BDNF, TrkB. BDNF binding to TrkB induces activation of several intracellular signaling cascades like MAPK, PI3K, phospholipase C-γ. It has been proposed that BDNF affects on cocaine reward are mainly due to activation of TrkB on D2-expressing MSNs, since specific TrkB gene deletion induces a decrease in cocaine-induced place preference and profound neuronal firing modifications [1].

Here, we seek to understand the rapid, acute effects of BDNF in the NAcore on drug seeking, using the behavioral model of cocaine self-administration in rats. To study the non-transcriptional effects of BDNF in the NAcore, rats were trained to self-administer cocaine and extinguished. We then microinjected BDNF into NAcore 15 min before cue-induced reinstatement. BDNF decreased reinstated lever pressing. Concurrently to this acute effect, we also measured a long-lasting inhibitory effect that endured for days after BDNF administration that is likely due to transcriptional changes. Supporting a role for endogenous BDNF-induced activation of TrkB we found that blocking TrkB activation by microinjecting TrkB-Fc 15 min before reinstatement potentiated reinstated lever pressing. TrkB-Fc also prevented co-administered BDNF from antagonizing reinstated cocaine seeking. BDNF effects seem specific to cue-induced drug seeking, since no decrease in exploratory behavior or cocaine-induced locomotion was observed after BDNF microinjections in the NAcore.

These results suggest that, in addition to the long-lasting transcriptional effects of BDNF shown in the literature, acute activation of the TrkB intracellular pathway just before reinstatement can prevent cocaine seeking.

Reference


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