BDNF is a member of the neurotrophic factor family and is the most abundant neurotrophin in the brain. BDNF plays a key role in the neuronal plasticity and survival of midbrain dopaminergic neurons. Evidence from animal and clinical studies suggests that increased brain BDNF activity may be implicated in the pathogenesis of substance abuse. For example, BDNF infusion into the rat midbrain enhances the rewarding effects of cocaine, as measured by the condition preference paradigm, and cocaine-conditioned place preference was reduced in heterozygous BDNF-knockout mice. Using a rat model of drug craving, it was found that the responsiveness to cocaine cues progressively increased over the first 60 days of cocaine withdrawal, and that BDNF levels within the mesolimbic system progressively increased after cocaine withdrawal. This suggests that increases in BDNF levels may lead to synaptic modifications that underlie enhanced responsiveness to cocaine cues after prolonged withdrawal periods.

Similarly, a single intra-VTA infusion of BDNF induced a long-lasting enhancement of cocaine seeking for up to 30 days, suggesting that BDNF-mediated neuroadaptations in the midbrain are involved in cocaine-seeking behavior after withdrawal. In humans, the 66Val allele of the BDNF Val66Met polymorphism is associated with higher BDNF secretion in response to neuronal stimulation compared with the 66Met allele. We found a higher BDNF 66Val homozygote frequency in individuals with drug use disorder as compared with normal controls.

In the nervous system, the proteolytic cleavage of pro-BDNF, a BDNF precursor, to (mature) BDNF occurs specifically through the tPA/plasmin pathway. Given that pro-BDNF and mature BDNF have distinct and sometimes opposing functions, the processing of these molecules in the tPA/plasmin pathway is central to determining the direction of BDNF action in neuronal plasticity. Thus, the increased tPA levels or activity might pose a conflict of interest.

**References**


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