Neurobiology of Adolescent Substance Use Disorders

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KEYWORDS

• Adolescence • Addiction • Neurobiology • Development • Substance use

KEY POINTS

- Subcortical reward processes are stronger in adolescents than adults, but prefrontal cortical executive control systems are weaker.
- Peer influences enhance reward-related neural responses of adolescents and increase sensation-seeking, risky behavior.
- Adolescents are more susceptible to stress, and some turn to substance use as a coping strategy.
- Adolescents are less sensitive to some of the acute negative consequences of substance use that can serve as a signal to limit intake, but more sensitive to long-term problems such as neurodegeneration and cognitive deficits.

INTRODUCTION

Developmental tasks of adolescence include emotional maturation, individuation, establishment of meaningful relationships outside the family, and progress toward independence from the family of origin. In this context, typical adolescent characteristics, including increased appetitive drives, sensory-seeking behavior, and experimentation, likely serve an adaptive function. These tendencies lead to increased risk-taking behaviors, including experimentation with substance use, as a common part of the adolescent experience. In fact, experimentation with drugs and alcohol can be considered a normative behavior, and only a fraction of those who experiment with drugs and alcohol go on to develop substance use disorders. In a longitudinal study of 101 subjects, it was found that those who experimented with drug use during adolescence had better "psychological health" than adolescents who either abstained completely or used substances frequently.[1]

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For numerous reasons, adolescence is a remarkably vulnerable time, characterized by changes in physiology, cognition, environmental influence, and social dynamics. Biological changes, mostly hormonally mediated, include physical growth, development of secondary sex characteristics, and alterations in neurobiology. Physiologic vulnerability to stress increases.[2,3] Some aspects of cognition begin to mature, whereas other aspects, particularly executive functioning, lag behind. External demands begin to exert more influence, including academic pressures, employment, and generally increased levels of responsibility. Peer influence and approval become more important, and social focus shifts away from the family of origin. Many psychiatric disorders have their onset in adolescence, including depression, anxiety, and substance use disorders. For adolescents who do engage in substance use, it is known that earlier onset of use is a significant predictor of development of a substance or alcohol use disorder over the lifetime, as well as predicting greater addiction severity.[4,5]

REVIEW OF NEUROBIOLOGY OF SUBSTANCE USE

Of all psychiatric disorders, the pathophysiology of addiction is perhaps the best understood. Only a small fraction of the millions of known chemical compounds support addictive behavior, and yet drugs of abuse have a startling diversity of chemical structures, including, for example, complex aromatic cannabinoids, opioid peptides, modified catecholamines, and even extremely simple molecules such as ethanol and nitrous oxide. The one property all these compounds share is that they cause dramatic increases in dopamine release within the nucleus accumbens.[6] Other salient rewards, such as food, sex, and other pleasurable activities, also cause dopamine release in the nucleus accumbens; indeed this dopaminergic activity is likely necessary for instigating and supporting all motivated behaviors that are aimed at repeating pleasurable experiences. The critical difference from these other rewards is that drugs of abuse stimulate accumbal dopamine release through *pharmacological*, as well as psychological, mechanisms.

ROLE OF NUCLEUS ACCUMBENS

The nucleus accumbens is the major component of the ventral striatum. It is a part of the basal ganglia, which is a set of subcortical structures that serve as a critical interface between limbic and motor circuitry, essentially allowing emotional responses to be translated into motor activity. Nucleus accumbens projection neurons send information through iterative cortico-striatal-thalamic loops, where neural activity is repeatedly modulated by afferents from multiple brain areas before ultimately exiting into the motor system to produce motivated behavior.[7] Glutamatergic projections carry information from a number of different structures to the nucleus accumbens, including processed multimodal sensory information from the amygdala, and contextual memory information from the hippocampus. Importantly, the prefrontal cortex provides executive control and decision-making information to the nucleus accumbens, and these prefrontal cortical afferents serve as a major source of inhibitory control over subcortical impulses, including urges to use drugs.[8] A relatively small group of brainstem neurons known as the ventral tegmental area provides dopaminergic input to the nucleus accumbens. Dopamine does not directly influence action potentials. Rather, it modifies neuronal responses to specific glutamatergic inputs. One long-lasting consequence of drug-induced spikes in accumbal dopamine is an alteration of synaptic density within this structure, such that specific circuits associated with