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HOT TOPICS

Guidance cues: linking drug use in adolescence with psychiatric disorders

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Adolescent onset of drug use is associated with an enduring elevation in the risk of progressing from recreational use to addiction. Unfortunately, adolescent experimentation with drugs of abuse remains common, with more than half of initiates under the age of 18 years old. This peak age for drug initiation coincides with a critical developmental period for reward-relevant substrates. Most notably, mesocorticolimbic dopamine circuitry is uniquely sensitive to disruption by drugs in adolescence, resulting in lasting behavioral changes linked to addiction vulnerability [1].

Our recent work in rodents highlights a novel role for guidance cues in (a) the adolescent establishment of mesocorticolimbic dopamine connectivity and cognitive processing and (b) the enduring effects of drugs of abuse on these events. First, we discovered that dopamine axons still grow to the prefrontal cortex (PFC) in adolescence [2]. This is the first concrete demonstration of long-distance axon growth in late postnatal development, which entails targeting decisions by dopamine axons en route to their final postsynaptic partners. Axon targeting relies on the interaction of extracellular guidance cues and their receptors. We find that the guidance cue Netrin-1 and its receptor DCC dictate dopamine axon targeting in adolescence. Specifically, mesolimbic dopamine axons have high levels of DCC and recognize the nucleus accumbens as their final target in adolescence. In contrast, mesocortical dopamine axons have little or no DCC and therefore fail to recognize this region as their final target and grow to the PFC instead. Reduced DCC expression in mesolimbic dopamine axons induces targeting errors in the nucleus accumbens and their ectopic growth to the PFC. By segregating dopamine innervation to cortical or non-cortical regions, DCC receptors organize PFC structure and function, including cognitive behaviors that are altered in addiction [2].

Second, we demonstrated that repeated non-contingent exposure to amphetamine in adolescence, at a dose resembling human recreational use, downregulates DCC expression in dopamine neurons [3]. This perfectly positions DCC signaling to mediate the enduring neuroanatomical and behavioral consequences of adolescent drug use. Indeed, amphetamine in early adolescence leads to an increase in the span of dopamine innervation to the PFC. However, it also leads to disorganized synaptic contacts and reduced dopamine turnover in adulthood [4, 5]. These alterations, in turn, produce deficits in behavioral inhibition and exaggerated salience attribution to drug-paired contexts; two behaviors associated with addiction susceptibility [4, 5].

Our findings indicate that DCC signaling wires the adolescent PFC and contributes to amphetamine-induced susceptibility to addiction. Interestingly, amphetamine down-regulates DCC via micro-RNAs, which are important biomarkers and mediators of psychiatric conditions [3]. Furthermore, variations in DCC expression occur in humans and lead to altered mesocorticolimbic connectivity [6]. Our work therefore contributes a novel perspective to the ongoing efforts of developing prevention and treatment strategies for addiction. The DCC pathway represents a promising site for targeted intervention during adolescence both to counteract detrimental effects of early drug use and promote healthy brain development.

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ADDITIONAL INFORMATION

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