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MEETING ABSTRACT

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Amphetamine in adolescence alters the expression of the dopamine gene, *Dcc,* and its microRNA regulators

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Initiation of drug use in adolescence is a strong predictor of the incidence and severity of addiction throughout life. Adolescence is a period of dynamic refinement in the organization of prefrontal cortex (PFC) circuitry, with dramatic changes occurring in the establishment of dopamine connectivity. We have shown that the guidance cue receptor DCC, which is highly expressed by dopamine neurons, orchestrates the dopamine innervation to the medial PFC (mPFC) specifically in adolescence. Importantly, we showed that exposure to amphetamine (AMPH) in adolescence, but not in adulthood, (a) downregulates DCC protein expression within ventral tegmental area (VTA) dopamine neurons, (b) leads in turn to increased mPFC dopamine input, but to a drastic reduction in mesocortical dopamine axons presynaptic sites, and (c) causes exaggerated salience attribution to a previously drug-paired environment. However, how AMPH in adolescence regulates DCC protein expression in dopamine neurons is currently unknown. Here, we sought to investigate whether AMPH in adolescence alters *Dcc* mRNA expression in the VTA and whether epigenetic mechanisms are involved. To this end, we treated adolescent C57BL/6 mice with saline or with the exact same AMPH regimen (4 mg/kg, one injection per day, every other day, from PND 21 ± 1 to PND 31 ± 1) that downregulates DCC expression and disrupts PFC dopamine development [1,2]. One week later, we measured *Dcc* mRNA expression in the VTA using real time PCR. Consistent with the effects of AMPH on DCC protein expression in adolescence, we found a significant reduction in VTA *Dcc* mRNA expression in AMPH-treated mice in comparison to saline-treated controls. Remarkably, this reduction was accompanied by increased expression of a microRNA which is expressed by dopamine neurons and is known to repress *Dcc* expression in the rodent and human brain. We are currently performing *in situ* hybridization to determine coexpression of *Dcc* and the microRNA in VTA dopamine neurons. We are also assessing whether exposure to environmental enrichment in adolescence alters *Dcc* and its epigenetic regulators, potentially protecting and/or reversing enduring detrimental effects of stimulant drugs of abuse.

References

1. Yetnikoff L, Almey A, Arvanitogiannis A, Flores C: **Abolition of the behavioral phenotype of adult netrin-1 receptor deficient mice by exposure to amphetamine during the juvenile period.** *Psychopharmacology,* 2011; 217(4):505–514. doi:10.1007/s00213-011-2312-6
2. Reynolds LM, Makowski CS, Yogendran SV, Kiessling S, Cermakian N, Flores C: **Amphetamine in adolescence disrupts the development of medial prefrontal cortex dopamine connectivity in a DCC-dependent manner.** *Neuropsychopharmacology,* 2015; 40(5):1101–1112. doi:10.1038/npp.2014.287

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