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Nico-teen: Neural substrates that mediate adolescent tobacco abuse.

Laura O'Dell, *University of Texas at El Paso*

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NICO-TEEN: Neural Substrates that Mediate Adolescent Tobacco Abuse

Adolescents are especially likely to initiate tobacco use and are more vulnerable to long-term tobacco dependence. Although the importance of factors such as environmental conditions, genetics, sex differences, and constituents of tobacco other than nicotine has been recognized, relatively little is known about the neural mechanisms that mediate enhanced sensitivity to tobacco abuse during adolescence.

Recent preclinical studies have led to our working hypothesis that enhanced tobacco abuse during adolescence is promoted by: (1) enhanced positive effects of nicotine; and (2) reduced negative effects of nicotine and withdrawal from this drug during adolescence compared with adulthood (O'Dell, 2009). Thus, the inadequate balance favoring strong positive effects of nicotine over reduced negative effects produces enhanced vulnerability to tobacco abuse during adolescence.

Much work comparing age differences to nicotine has focused on the mesolimbic dopamine pathway from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc) where dopamine is increased by nicotine but decreased during withdrawal (Mansvelder and McGehee, 2002). These neurochemical effects are age dependent, as nicotine increases NAcc dopamine to a greater extent in adolescent *vs* adult rats (Shearman *et al*, 2008). Also, we reported that nicotine withdrawal decreases NAcc dopamine to a lesser extent in adolescent *vs* adult rats (Natividad *et al*, 2010). These studies suggest that mesolimbic dopaminergic mechanisms are important in modulating adolescent vulnerability to tobacco abuse.

Our working hypothesis is that the age differences in dopamine have their origin in the VTA in which excitatory mechanisms regulate dopamine release in the NAcc. This is based on our observation that nicotine withdrawal decreases glutamate levels in the VTA of adult, but not adolescent, rats. Because excitation in the VTA is not reduced, adolescents show smaller reductions in NAcc dopamine during withdrawal. This hypothesis is consistent with evidence that excitatory systems that facilitate dopamine are overdeveloped during adolescence (McDonald and Johnston, 1990). Taken together, we hypothesize that adolescents show enhanced nicotine reward and reduced withdrawal through enhanced excitation of VTA cell bodies that release dopamine in the NAcc.

Our hypothesis has important clinical implications. First, reduced sensitivity to withdrawal during adolescence implies that the diagnostic criteria developed for tobacco dependence in adults, based primarily on withdrawal, are inappropriate for adolescents. A corollary is that treatments focusing on alleviating withdrawal will probably fail in adolescents, a hypothesis supported by a study comparing adolescent and adult smokers (Smith *et al*, 2008). Our neurochemical data also suggest that adolescents may be less sensitive to current treatments that facilitate dopamine (such as Zyban), as they may not show deficits in dopamine during withdrawal. Given the strong rewarding effects of nicotine during adolescence, the best strategy for reducing tobacco abuse may be to strictly reduce access to nicotine-containing products during this developmental period. Furthermore, pharmacological treatments for adolescent smokers may target the strong rewarding effects of nicotine that appear to be mediated through mesolimbic dopamine and upstream glutamatergic mechanisms that modulate this reward pathway. Future work is needed to validate the role of these mechanisms in adolescent tobacco abuse, and to examine whether they also mediate long-term vulnerability to tobacco abuse in adults that initiated smoking during adolescence.

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Laura E O'Dell[1]

[1]Department of Psychology, The University of Texas at El Paso, El Paso, TX, USA
E-mail: lodell@utep.edu

DISCLOSURE

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