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Review

Age-related changes in prefrontal norepinephrine transporter density: The basis for improved cognitive flexibility after low doses of atomoxetine in adolescent rats

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ABSTRACT

Adolescence is a period of major behavioral and brain reorganization. As diagnoses and treatment of disorders like attention deficit hyperactivity disorder (ADHD) often occur during adolescence, it is important to understand how the prefrontal cortices change and how these changes may influence the response to drugs during development. The current study uses an adolescent rat model to study the effect of standard ADHD treatments, atomoxetine and methylphenidate on attentional set shifting and reversal learning. While both of these drugs act as norepinephrine reuptake inhibitors, higher doses of atomoxetine and all doses of methylphenidate also block dopamine transporters (DAT). Low doses of atomoxetine, were effective at remediating cognitive rigidity found in adolescents. In contrast, methylphenidate improved performance in rats unable to form an attentional set due to distractibility but was without effect in normal subjects. We also assessed the effects of GBR 12909, a selective DAT inhibitor, but found no effect of any dose on behavior. A second study in adolescent rats investigated changes in norepinephrine transporter (NET) and dopamine beta hydroxylase (DBH) density in five functionally distinct sub-regions of the prefrontal cortex: infralimbic, prelimbic, anterior cingulate, medial and lateral orbitofrontal cortices. These regions are implicated in impulsivity and distractibility. We found that NET, but not DBH, changed across adolescence in a regionally selective manner. The prelimbic cortex, which is critical to cognitive rigidity, and the lateral orbitofrontal cortex, critical to reversal learning and some forms of response inhibition, showed higher levels of NET at early than mid- to late adolescence.

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1. Introduction

There is an increasing awareness that disruption of the development of prefrontal cortex in adolescence increases vulnerability to a multitude of neuropsychiatric disorders (Casey and Jones, 2010; Andersen, 2008). Moreover the diagnoses of disorders such as attention deficit hyperactivity disorder (ADHD) that are made in childhood require pharmacologic treatment for prolonged periods to improve attention and to decrease vulnerability to substance abuse related to impaired impulse control (Mannuzza et al., 2008; Szobot and Bukstein, 2008). Though much of the literature has examined the impact of these drugs on dopaminergic systems (Somkuwar et al., 2013), many of these agents also affect noradrenergic neurotransmission in the prefrontal cortex and this action has been hypothesized to be a major factor underlying the clinical efficacy of these compounds (Berridge et al., 2006, 2012; Devilbiss and Berridge, 2008; Agster et al., 2011). Two commonly prescribed medications for ADHD, atomoxetine and methylphenidate, share a common mechanism of blocking norepinephrine transporters (NET) thus prolonging the availability of extracellular norepinephrine. As NET is a target for drugs used to treat ADHD (Chamberlain et al., 2007; Cabellero and Nahata, 2003), it is imperative that we: 1) differentiate the effects of dopamine and norepinephrine reuptake blockade on executive functions in adolescents and 2) understand how substrates for the actions of these drugs, e.g. NET, change in prefrontal cortical sub-regions across development.

To address these questions, the current study was designed in two parts. The first was to compare the effects of drugs that block NET, DAT or both on the behavior of adolescent rats in an attentional set-shifting paradigm that allows assessment of reversal learning, response inhibition, distractibility, as well as the formation and shifting of an attentional set (Birrell and Brown, 2000; Robbins et al., 1998). These tests model behavior in humans (Owen et al., 1991), and are amenable to use in non-human primates (Roberts et al., 1992; Roberts and Wallis, 2000) and rodents (Danet et al., 2010; Tait et al., 2007) thus facilitating cross-species translation of findings. Normal subjects show flexible attentional control that allows for focused attention but can also respond when response contingencies have changed (Aston-Jones and Cohen, 2005; Bouret and Sara, 2005). Cognitive rigidity is the inability of subjects to disengage from focused attention to learn new response contingencies (McGaughy et al., 2008; Newman et al., 2008; Newman and McGaughy, 2011a) whereas distractibility results when subjects cannot adequately focus attentional scope. Prior work with adolescent rats revealed immaturities in cognitive control when compared to adults (Newman and McGaughy, 2011b). These data support the hypothesis that maturation of different aspects of cognitive control occur independent of one another with the ability to shift an attentional set developing prior to