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Review article

ADHD, altered dopamine neurotransmission, and disrupted reinforcement processes: Implications for smoking and nicotine dependence

Scott H. Kollins [a,*], R. Alison Adcock [a,b]

[a] Department of Psychiatry & Behavioral Science, Duke University School of Medicine, Durham, NC, USA
[b] Duke Center for Cognitive Neuroscience, Duke University, Durham, NC, USA

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is a common and impairing disorder affecting millions of children, adolescents, and adults. Individuals with ADHD smoke cigarettes at rates significantly higher than their non-diagnosed peers and the disorder also confers risk for a number of related adverse smoking outcomes including earlier age of initiation, faster progression to regular use, heavier smoking/greater dependence, and more difficulty quitting. Progress in our understanding of dopamine neurotransmission and basic behavioral reinforcement processes in ADHD may help increase our understanding of the ADHD-smoking comorbidity. This review will examine how these areas have been studied and how further work may aid in the development of better prevention and treatment for smoking in those with ADHD.

Contents

1. Introduction

Attention deficit hyperactivity disorder (ADHD) affects millions of children and adults in the US and is a significant independent risk factor for smoking (Kessler et al., 2006; Lambert and Hartsough, 1998; Milberger et al., 1997a, 1997b; Molina and Pelham, 2003; Pomerleau et al., 1995; Visser et al., 2007). Individuals with ADHD start smoking

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; DRD4, Dopamine D4Receptor; DRD5, Dopamine D5Receptor; DRD2, Dopamine D2Receptor; DAT, Dopamine Transporter; DBH, Dopamine Beta-Hydroxylase; PET, Positron Emission Tomography; VTA, Ventral Tegmental Area; MAO-A, Monomine Oxidase A.

* Corresponding author at: 2608 Erwin Road, Suite 300, Durham, NC 27705, USA. Tel.: +1 919 681 0014.
E-mail address: scott.kollins@duke.edu (S.H. Kollins).

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at an earlier age and become more dependent (Milberger et al., 1997a; Wilens et al., 2008). Moreover, individuals with ADHD or high levels of ADHD symptoms are also more likely to progress from smoking experimentation to regular use (Rohde et al., 2004). For example, we found that high levels of ADHD symptoms in a population-based sample were associated with progression from experimentation or no use in the teenage years to daily smoking in the early 20s (Fuemmeler et al., 2007). Given the extraordinary morbidity and mortality associated with cigarette smoking (CDC, 2002), the high rate of smoking observed among those with ADHD is therefore a significant public health issue. A clearer understanding of the factors that increase risk for smoking in those with ADHD would be an important step towards preventing and treating smoking in this high-risk group.

The association between ADHD and smoking is complex and involves multiple stages (McClernon and Kollins, 2008), although the precise mechanisms conferring risk have not been thoroughly elucidated. Convergent evidence suggests that dopamine-mediated disruptions in reinforcement processes are involved in key aspects of smoking behavior among individuals with ADHD. The overall goal of the present review is to consider the evidence for the role of dopamine and reinforcement processes in increased risk for smoking and related outcomes in patients with ADHD. The review will be organized as follows. First, we will review both historical and current perspectives on the role of dopamine functioning in ADHD. Second, we will consider evidence implicating disrupted reinforcement processes in ADHD. We will then discuss the few studies that have explicitly linked dopaminergic dysfunction to altered reinforcement processes in ADHD. The relevance for this association to understanding smoking risk in individuals with ADHD will then be evaluated. We will conclude with suggestions for future research in this area.

2. Dopamine and ADHD

2.1. Historical perspectives on catecholamine function in ADHD

For decades, researchers and clinicians have speculated about the role of disrupted neurotransmission and subsequent reinforcement processes as key features of ADHD. Paul Wender, an early pioneer in the study of ADHD and its treatment, wrote in 1973 that minimal brain dysfunction (MBD; a nosological precursor to ADHD) was "characterized by…a diminished sensitivity to positive and negative reinforcement," and "…that these deficits are secondary to disorders of monoamine metabolism and that such disorders may occur on a genetic basis"(Wender, 1973). This reasoning was supported by several clinical and scientific observations: 1) MBD and related problems were likely to run in families; 2) stimulant drugs were effective for improving behavior problems in children with MBD and related difficulties (Bradley, 1937); and 3) that these same drugs facilitated monoamine neurotransmission in animals (Schildkraut and Kety, 1967; Wender et al., 1971). In the 40 years since Wender's prescient speculation, significant progress has been made that provides support for his hypotheses. We will briefly consider the evidence for the genetic basis of ADHD (with emphasis on genes associated with dopamine neurotransmission) and the direct measurement of dopamine neurotransmission in individuals with ADHD.

2.2. Genetic studies of ADHD — links to dopamine function

As Wender noted, it has long been observed that problems associated with ADHD run in families. Family, twin, and adoption studies all provide strong support for the genetic basis of the disorder, with heritability estimates from twin studies as high as 0.7–0.8 (Faraone et al., 2005). Since the mid-1990s, several hundred candidate gene studies have been conducted to isolate specific variants conferring risk for the disorder. Although these studies have often been characterized by small effect size and failures to replicate, several gene variants have consistently been shown to increase risk for ADHD. Perhaps not surprisingly, most of these candidate genes are involved in catecholamine function generally, and dopamine function specifically. In one meta-analysis, seven candidate genes were identified that demonstrated significant pooled odds ratios for conferring risk for ADHD across at least 3 separate studies. Of these, 5 of the genetic variants were explicitly involved in dopamine neurotransmission: 2 variants of the dopamine D_4 receptor gene (DRD4), the dopamine D_5 receptor gene (DRD5), the dopamine transporter gene (DAT) and the dopamine beta-hydroxylase gene (DBH) (Faraone et al., 2005). More recently, a meta-analysis specifically focused on dopamine receptor genes (D1–D5), found associations between variants of the DRD4 gene, the DRD5 gene, and the dopamine D_2 (DRD2) gene and risk for ADHD, although due to heterogeneity, findings for the DRD2 gene were deemed to be invalid (Wu et al., 2012). Although genome-wide linkage and association studies of ADHD have generally not found evidence for the involvement of regions relevant to dopamine neurotransmission (Faraone and Mick, 2010), the results of candidate gene studies provide some support for dopamine-related genes as contributors of risk, albeit small, for the development of ADHD.

2.3. Functional role of dopamine gene variants implicated in ADHD

Although the functional role of specific dopamine gene variants implicated in ADHD has been partially characterized in nonhuman species and in vitro, work in humans has been more limited. The most common variant of the DRD4 gene associated with ADHD is a VNTR polymorphism in exon III of the gene, specifically a 7-repeat polymorphism. This variant has been shown to cause a blunted dopaminergic response as compared to other (e.g., 4-repeat, 2-repeat) variants (Asghari et al., 1995; Van Tol et al., 1992). In humans, the 7-repeat variant of DRD4 has been linked to differences in ventral striatal activity during reward tasks (Forbes et al., 2009; Nikolova et al., 2011).

The DRD5 gene is expressed widely in CNS and has a significantly higher affinity for dopamine than the DRD1 gene, despite strong similarity in membrane structure (Wu et al., 2012). In general, the DRD5 gene is thought to modulate hypothalamic function and aspects of motor control (Apostolakis et al., 1996; Rivkees and Lachowicz, 1997; Sibley, 1999). The specific functional role of the variant that has been associated with ADHD – a 148-bp allele located in18.5 kb at the end of the 5′ flank – is not known (Wu et al., 2012).

Variations in the dopamine transporter gene (DAT1/SLC6A3) have been implicated in striatal dopamine function in both human and in vitro studies, though findings are somewhat mixed (Heinz et al., 2000; van de Giessen et al., 2009; VanNess et al., 2005). The 10-repeat variant of a VNTR polymorphism in the 3′ untranslated region of the gene is most often implicated in the presentation of ADHD, and some studies have reported that 9-repeat carriers of this variant express higher levels of striatal dopamine, while other studies have reported that 10-repeat carriers express more DAT (Heinz et al., 2000; VanNess et al., 2005). Animal models that either knock down or knock out the DAT transporter altogether present with many ADHD-like phenotypes, including increased activity levels that are normalized to wild type levels with stimulant administration (Gainetdinov et al., 1999; Giros et al., 1996; Zhuang et al., 2001).

The DBH gene is involved in the enzymatic pathway that controls the conversion of dopamine to norepinephrine. Several mutations of this gene have been shown to result in DBH deficiency, a relatively rare condition in which low levels of norepinephrine cause difficulty regulating blood pressure and other autonomic nervous system problems (Senard and Rouet, 2006). The specific variant of the DBH gene most widely studied in ADHD is a TaqI polymorphism in the 5th intron (Daly et al., 1999; Faraone et al., 2005). Although this variant has been reported to confer risk for other psychiatric/behavioral conditions (e.g., smoking, schizophrenia) (Freire et al., 2006; Wei et al., 1998), the specific function of this polymorphism has not been reported.