Neurosci Bull April 1, 2015, 31(2): 227–234. http://www.neurosci.cn
DOI: 10.1007/s12264-014-1514-4

·Review·

Prefrontal cortical α_{2A}-adrenoceptors and a possible primate model of attention deficit and hyperactivity disorder

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Attention deficit and hyperactivity disorder (ADHD), a prevalent syndrome in children worldwide, is characterized by impulsivity, inappropriate inattention, and/or hyperactivity. It seriously afflicts cognitive development in childhood, and may lead to chronic under-achievement, academic failure, problematic peer relationships, and low self-esteem. There are at least three challenges for the treatment of ADHD. First, the neurobiological bases of its symptoms are still not clear. Second, the commonly prescribed medications, most showing short-term therapeutic efficacy but with a high risk of serious side-effects, are mainly based on a dopamine mechanism. Third, more novel and efficient animal models, especially in nonhuman primates, are required to accelerate the development of new medications. In this article, we review research progress in the related fields, focusing on our previous studies showing that blockade of prefrontal cortical α_{2A}-adrenoceptors in monkeys produces almost all the typical behavioral symptoms of ADHD.

Keywords: prefrontal cortex; α_{2A}-adrenoceptors; cognitive functions; attention deficit and hyperactivity disorder; animal models

Introduction

Attention deficit and hyperactivity disorder (ADHD) is one of the most prevalent childhood neurodevelopmental conditions, affecting 3–5% of grade-school children worldwide[1]. It is characterized by inappropriate levels of inattention, impulsivity, and/or hyperactivity[2-4]. These symptoms develop in childhood, and can persist into adolescence and adulthood[5]. ADHD seriously affects cognitive development[6-8], and, without appropriate treatment, has consequences for the risk of anxiety, substance abuse, and depression in adulthood[2, 5, 9].

The neurobiological bases of ADHD symptoms are still not clear[10]. Clarifying them can help better understand the biological vulnerabilities that may underlie ADHD in a specific patient and how to modulate the responses to treatment, thereby contributing to better and more effective therapy.

It has been suggested that the symptoms involve a dopaminergic mechanism in the prefrontal cortex (PFC) and striatum[11, 12]. Experimentally decreased dopamine (DA) release in the PFC results in ADHD-like symptoms[13, 14]. To date, DA dysregulation is thought to be central to the neurobiology of ADHD, and its pharmacological treatment, such as methylphenidate (MPH, i.e. Ritalin)[15-17], levels the DA concentration in the synapse and extrasynaptic space in the PFC as a blocker of the DA transporter. MPH ameliorates inappropriate inattention[18-20], decreases impulsivity[21], and enhances inhibitory control[22]. However, as MPH is a prescription psychostimulant, there are strong concerns over drug dependence, paranoia, schizophrenia, and behavioral sensitization that might be caused by long-term therapy, similar to other stimulants[23-25].

Converging evidence indicates that the patho-physiology of ADHD has multiple origins[26-32]; for instance, norepinephrine (NE) has long been implicated[33, 34]. In this paper, we review research progress in the relevant fields, focusing on the potential relationship between prefrontal α_{2A}-adrenoceptors and ADHD in nonhuman primates[35-39].

Prefrontal Cognitive Dysfunctions in ADHD

The PFC plays a key role in cognitive functions such as working memory, the regulation of attention, and behavioral inhibition. Imaging and neuropsychological studies have shown that patients with ADHD have poor PFC functions, including poor attention regulation[40], limited working memory[41], and inability to inhibit inappropriate motor activity[42].

Working memory is a fundamental higher-order function, underlies a wide range of executive functional processes[43, 44], and is primarily controlled by the PFC[45, 46]. It has been shown that ADHD patients have altered architecture and less activation in the PFC[47-49]. Persistent working-memory problems are the main cognitive deficit in ADHD[40, 41, 50, 51].

Attention brings sensory or mental stimuli to the forefront of awareness[40, 52], and plays a pivotal role in mediating the executive functions of the PFC. During distracted states, the capacity to diminish the awareness of relevant stimuli is compromised. Compared to normal peers, ADHD patients show attention deficits in detecting invalidly-cued targets with slower speed and less accuracy[53, 54].

Inhibitory control of behavior is one of the most important functions of the PFC[55]; ablation or lesion of the frontal cortex in monkeys induces locomotor hyperactivity[56-58]. Perhaps the most fundamental deficit in ADHD is the lack of response inhibition[52]. In laboratory studies of tasks that measure inhibitory control, children with ADHD often perform more poorly than both normal controls and children with other psychiatric disorders[59, 60]. Schulz *et al.* reported that response inhibition in adolescents diagnosed with ADHD is primarily mediated by fronto-striatal circuitry[61, 62].

Prefrontal α_{2A}-Adrenoceptor Blockade Produces ADHD Phenotypes

ADHD has been posited to be caused by hypofunctional catecholamine systems[63] in multiple brain regions including the PFC[64-66] and striatum[67]. Implicated in this are NE projections that originate primarily from neurons in the locus coeruleus and send projections to multiple regions, including the PFC[68]. There are many subtypes of adrenergic receptors in the PFC, including the α_{2A} subtype. The α_{2A}-adrenoceptors are localized at both pre- and post-synaptic NE terminals[69]. However, studies in rodents, monkeys, and humans have shown that lower to moderate levels of NE have a beneficial influence on prefrontal cognitive functions through action at post-synaptic α_{2A}-adrenoceptors[64, 70].

ADHD symptoms can be mimicked by blockade of α_{2A}-adrenoceptors in the PFC. To investigate the role of prefrontal α_{2A}-adrenoceptors in the inhibitory control of behavior, we trained two monkeys to perform a go/no-go task, and the α_{2A}-adrenergic antagonist yohimbine was infused bilaterally and chronically into the dorsolateral PFC with mini-osmotic pumps. We found that blockade of the α_{2A}-adrenoceptors selectively impaired the “no-go” performance of monkeys, leaving the “go” performance intact. In quite a few cases, the monkeys should have kept their hands still and not touch the screen (no-go), but they made a response to the screen[38]. Infusion of saline at the same cortical locations did not affect the no-go performance, indicating that the yohimbine-induced impulse was not because of nonspecific factors such as infusion-induced cortical damage (Fig. 1A). Our previous work provided the first behavioral evidence that α_{2A}-adrenocepters in the dorsolateral PFC are involved in the inhibitory control of behavior.

In addition, the monkeys’ locomotor activity was monitored before, during and after yohimbine infusion into the dorsolateral PFC. Compared to that before administration, the daily locomotor activity increased dramatically during the 8-day administration of yohimbine; this gradually returned to normal after the infusion was stopped (Fig. 1B). Infusion of saline at the same location did not cause locomotor hyperactivity[39]. This work suggests that the α_{2A}-adrenoceptors in the dorsolateral PFC are associated with locomotor activity, and the dorsolateral PFC dysfunction of α_{2A}-adrenergic transmission could be one of the main causes of the impulsive behaviors and hyperactivity in children with ADHD.

Due to the limitations of working on nonhuman primates, we also implemented similar experiments on rats to assess the dose-dependent and age effects of yohimbine at a homological cortical site, the medial PFC. The results showed that yohimbine infused into the medial PFC dose-dependently induced hyperactivity in rats of different ages, and the trends showed that the younger the rats, the more hyperactivity

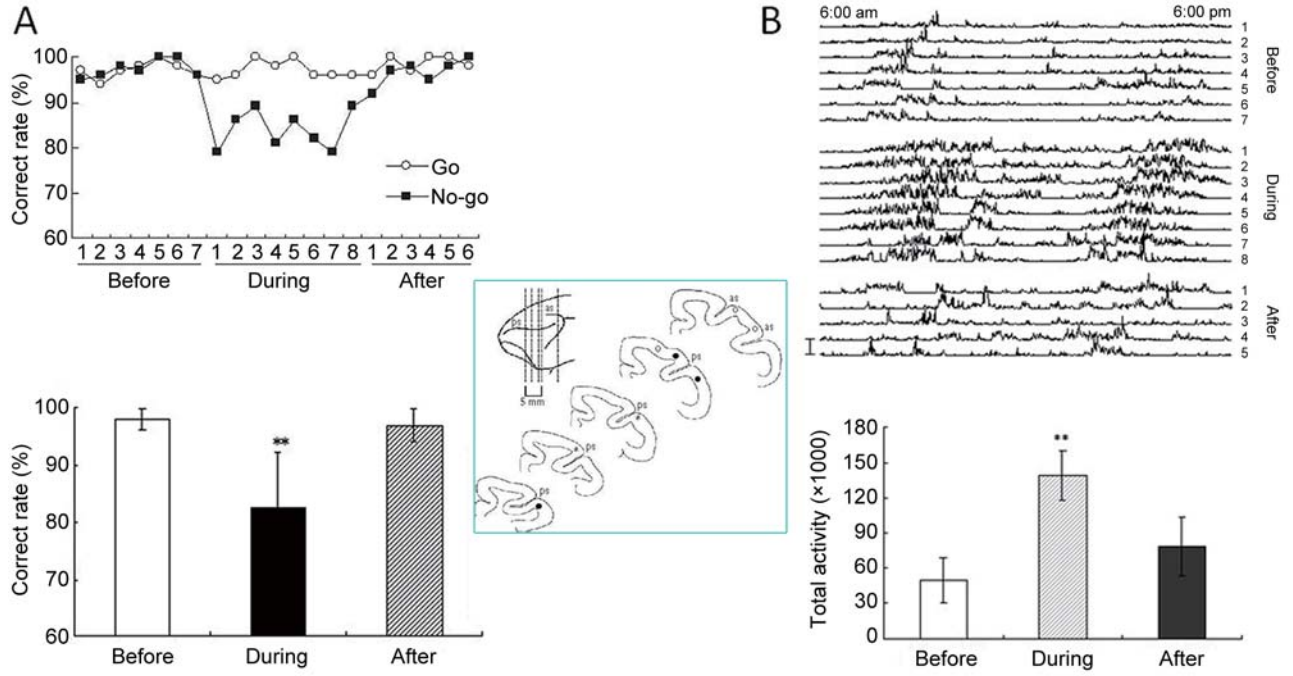

Fig. 1. Yohimbine infused bilaterally and chronically into the dorsolateral prefrontal cortex impairs impulse control and induces locomotor hyperactivity (adapted from Ma CL *et al.,* Neuroreport, 2003[38] and Biol Psychiatry, 2005[39]). (A) Yohimbine impairs "no-go" performance but has no effect on "go" performance. In several cases, the monkeys should not touch the screen (no-go), but they make a response. (B) Daily locomotor activity increases during administration of yohimbine. Each trace is a daily recording from 06:00 to 18:00. Inset: Reconstructed sites for chronic administration of yohimbine and saline. Filled symbols, yohimbine infusion; open symbols, saline infusion; as, arcuate sulcus; ps, principal sulcus.

presented at the same dose (unpublished data). All these results showed that dysfunction of the PFC α_{2A}-adrenoceptors results in the behavioral problems seen in ADHD.

ADHD symptoms can also be induced in humans by reducing the stimulation of α_{2A}-adrenoceptors. Kopeckova *et al.* investigated a polymorphism in the promoter region of the gene encoding DA beta-hydroxylase, an enzyme that reduces NE synthesis, and found that the affected children had poor sustained attention, weaker impulse control, and impaired executive function[71]. Genetic alterations in α_{2A}-adrenoceptors also impair PFC executive function, and lead to conditions seen in ADHD[72]. Thus, prefrontal α_{2A}-adrenoceptors are required for attention and behaviors in humans too.

Prefrontal α_{2A}-Adrenoceptor Stimulation Ameliorates Cognitive Dysfunctions in ADHD

Behavioral, pharmacological, and electrophysiological research has shown that stimulation of α_{2A}-adrenoceptors has a beneficial influence on PFC cognitive functions. Arnsten *et al.* found that systemic administration of the α_{2A}-adrenergic agonist guanfacine improves working memory in monkeys[73]. Steere demonstrated that systemic administration of guanfacine improves visual object discrimination reversal performance in aged rhesus monkeys[74]. Our work showed that both systemic administration and local infusion of guanfacine into the PFC improve visuomotor associative learning[70, 75]. Using an iontophoretic technique, stimulation of α_{2A}-adrenoceptors in the PFC was found to increase the spiking activity associated with working memory in behaving monkeys[37, 76].

Neuronal activity in the PFC associated with working memory can be enhanced by α_{2A}-adrenoceptor stimulation through cAMP-HCN signaling pathways[76, 77]. Our work suggested that under normal physiological conditions, the α_{2A}-adrenoceptors in pyramidal cells can be activated through Gi-cAMP-HCN signaling[78]. On the other hand,

under stress, activation of α_{2A}-adrenoceptors to protect PFC functions might occur *via* the Gi-cAMP-PKA-CaMKII-AMPAR signaling pathway[76]. Both mechanisms together optimize the synaptic inputs to pyramidal neurons and determine the synaptic outputs for PFC cognitive functions. Indeed, it has been reported that guanfacine at relatively high doses suppresses evoked excitatory postsynaptic currents, and has no enhanced effect or even suppresses delay-related activity[76].

New Insights to Develop a Primate Model of ADHD

As noted above, most of the commonly-prescribed medications for ADHD are psychostimulants, which are reported to have short-term therapeutic efficacy but with a high risk of serious adverse effects with long-term treatment. It is urgent to find new medications with high therapeutic efficacy and low adverse effects for children with ADHD. The first step now is to develop novel animal models of ADHD. A good model should very nearly show the fundamental behavioral characteristics of ADHD, conform to a theoretical rationale for ADHD, account for the neurobiology, and respond to therapeutic interventions both behaviorally and pharmacologically[79].

Currently, animal models of ADHD are genetic and non-genetic[80]. The spontaneously-hypertensive rat (SHR), the most widely used model, is a genetic model[81, 82]. SHRs exhibit hyperactivity[83, 84], impulsivity/inattention[82, 85], and poor learning and memory[86]. They also have disturbances in glutamate, DA, and NE functions, which in parallel demonstrate that ADHD patients have defects in the neuronal circuits required for reward-guided associative learning and memory formation[87]. Clearly, the SHR is a good model for the study of memory deficits in ADHD, primarily in the context of particular risk factors/symptoms, responsiveness to specific drugs or other treatments or biomarkers for the diagnosis of ADHD, and for understanding the pathological mechanisms for the development of therapeutic approaches. However, SHRs do not fulfill all the behavioral and pharmacological profiles of an ADHD model; for example, ADHD-like behaviors in SHRs are not restricted to males[88]. Hyperactive behavior in SHRs is ameliorated only by high doses of amphetamine or MPH[84], unlike ADHD patients, whose behavioral deficits can be improved with low doses of MPH. Importantly, ADHD patients show reduced regional cerebral blood flow in the frontal cortex[89], while SHRs do not[90,91].

Our previous research with monkeys indicates that blockade of the prefrontal α_{2A} receptors induces locomotor hyperactivity, impulsivity, and poor attention regulation/working memory. These results verify the feasibility and acceptability of treating ADHD by stimulating α_{2A}-adrenoceptors in the PFC or up-regulating the NE concentration in synapses and extrasynaptic space in the PFC. Actually, the α_{2A}-adrenergic agonists guanfacine and clonidine have been used experimentally and clinically to treat ADHD[92-97]. The selective inhibitor of the NE transporter atomoxetine (tomoxetine or LY139603) has also been reported to alleviate ADHD symptoms[98]. All these medications have achieved much better therapeutic efficacy with less adverse effects[99] than MPH and amphetamines, although there is controversy regarding the long-term effectiveness[100, 101].

Thus, in the future, studies should focus on developing a novel ADHD model in nonhuman primates, by down-regulating or blocking the α_{2A}-adrenoceptors in the dorsolateral PFC. This could be realized by chronic bilateral infusion of yohimbine. This kind of animal model could approximate the fundamental behavioral characteristics of ADHD, conform to a theoretical rationale for ADHD associated with prefrontal α_{2A}-adrenoceptors, and account for the neurobiology and therapeutic interventions in terms of both pharmacological and behavioral functions.

ACKNOWLEDGMENTS

This review was supported by grants from the National Natural Science Foundation of China (31460263, 30990263, and 31271171), and the National Basic Research Development Program (973 Program) of China (2013CB835101).

Received date: 2014-06-30; Accepted date: 2015-02-11

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