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TYPE:	Article CC:CCG
JOURNAL TITLE:	Current developmental disorders reports
USER JOURNAL TITLE:	Current Developmental Disorders Reports
ARTICLE TITLE:	Dopamine Receptor Expression and the Pathogenesis of Attention-Deficit Hyperactivity Disorder: a Scoping Review of the Literature
ARTICLE AUTHOR:	Dum, Rachel
VOLUME:	9
ISSUE:	4
MONTH:	01
YEAR:	2022
PAGES:	127-136
ISSN:	2196-2987
OCLC #:	

Processed by RapidX: 11/5/2023 6:37:57 PM

Current Developmental Disorders Reports (2022) 9:127–136
https://doi.org/10.1007/s40474-022-00253-5

ADHD (A AGGARWAL, SECTION EDITOR)

Dopamine Receptor Expression and the Pathogenesis of Attention-Deficit Hyperactivity Disorder: a Scoping Review of the Literature

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Accepted: 21 September 2022 / Published online: 3 October 2022

Abstract

Purpose of Review CNS stimulants have been the treatment of choice among children with attention-deficit hyperactivity disorder (ADHD) ages 6 and older, but their effectiveness and tolerability are major concerns. There is an unmet need for dopamine receptor-specific pharmacotherapy to improve the effectiveness and tolerability. Here, we conducted a scoping review of the literature to evaluate the current understanding of specific receptors and how they may relate to various phenotypes and behaviors in ADHD.

Recent Findings ADHD is the most common pediatric neurobehavioral disorder and is associated with significant impairment and long-term negative outcomes. The pathophysiology of ADHD is related to dopamine (DA) and dopamine receptor (DAR) dysregulation in the brain. There is growing evidence that specific dopamine receptor subtypes are associated with specific symptoms and behaviors associated with ADHD, such as motor and attention dysfunction.

Summary This study provides a scoping review of the up-to-date knowledge on specific DAR subtypes and how they may be implicated in the pathophysiology and or symptoms of ADHD. Knowledge of DAR and how they relate to the underlying disease process of ADHD may aid in developing targeted treatment options for ADHD with improved efficacy and tolerability.

Keywords ADHD · Dopamine · Dopamine receptor expression · ADHD pathophysiology

Introduction and Background

Attention-deficit hyperactivity disorder is a chronic neurobehavioral disorder that is characterized by hyperactivity, inattention, and impulsivity. ADHD remains the most common neurobehavioral disorder, affecting 5 to 7% of schoolchildren worldwide [1, 2] and up to 11% in the USA [2, 3]. More than 50% of youth with ADHD have comorbid psychiatric symptoms or diagnoses including mood disorders, irritability, aggression, and learning disabilities [2, 4]. ADHD symptoms not only impair functioning at home, school, and other social avenues, but also increase the risk for motor vehicle crashes, academic failure, occupational challenges, and suicidal behaviors [2, 5, 6]. There are multiple evidence-based pharmacological and psychosocial interventions for ADHD [5]. Pharmacologic treatment is the recommended treatment for ADHD for children 6 and older, and CNS stimulants are one of the most utilized pharmacological treatments [5]. Approximately 5% of school-aged children have been prescribed ADHD medication in the USA [2] and the national annual rate of stimulant dispensing has increased significantly from 5.6 to 6.1 prescriptions per 100 persons from 2014 to 2019 [7].

CNS stimulants such as methylphenidate enhance dopaminergic neurotransmission by directly inhibiting dopamine transporters (DAT) [8•]. Dopamine (DA) is a key catecholamine in the mammalian brain and plays a critical role in mediating neuronal motor control, cognition, emotion, vascular function, and event prediction [9••]. Previous imaging studies have identified that the main sites of action for methylphenidate are in brain regions with high concentrations of both DA and DA receptors (DAR), specifically the caudate,

This article is part of the Topical Collection on *ADHD*

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putamen, and basal ganglia [10]. Analysis of cerebral spinal fluid of children diagnosed with ADHD has both supported these imaging findings and revealed that DA metabolites are positively correlated with the degree of hyperactivity in patients [10].

CNS stimulants are effective; however, short- and long-term tolerability are major concerns [5, 11]. There is a clear need for improved ADHD pharmacologic treatment effectiveness, which may include strengthening dopaminergic neurotransmission without directly blocking DAT [8•]. Psychostimulants have non-selective action of dopaminergic functioning and generally increase the extracellular concentrations of monoamines, resulting in broad activation of many receptor subtypes. To develop targeted therapies for ADHD, which is widely accepted to be related to DA and dopaminergic receptor dysregulation [8•], it is important to study the many subtypes of DAR. Currently, there is little evidence in the literature that identifies specific DAR subtypes as targets for pharmacology in ADHD, and without clear pharmacologic mechanisms of action, specific therapeutic targets remain unknown [10]. This scoping review aims to summarize the most recent data on DAR-specific studies and identify gaps in the literature where it pertains to targeted ADHD treatment. Knowledge of DAR and how they relate to symptoms of ADHD may aid in developing targeted treatment options for ADHD with improved efficacy and tolerability.

Methods

We performed a multi-step search strategy. A limited preliminary search on PubMed and Google Scholar was first performed to identify the scope of relevant papers on this topic. We then analyzed the keywords of the titles and abstracts to choose the most relevant search terms. All authors discussed the terms and finalized the search strategy. Based on the output of the first step, two authors systematically searched the literature in the English language in PubMed, Scopus, Embase, and Web of Science Published from December 1995 to August 2022. We used the following keywords in our search ("ADHD" OR "Attention-Deficit-Hyperactivity-Disorder") AND ("Dopamine" OR "Dopamine-receptor"). Two authors (RR and AG) separately screened the title and abstracts of the documents and ruled out articles that were not relevant to dopamine-receptor role in ADHD pathophysiology. Discrepancies were resolved by discussion with the senior author (AB). We conducted a descriptive analysis of the characteristics of the included articles and performed a narrative synthesis of the results.

Review of Dopamine Receptor Types and Involvement in ADHD

There are five types of dopamine receptors (D1–D5); D2, D3, and D4 are inhibitory, while D1 and D5 are stimulatory in nature. We have summarized important findings in Tables 1 and 2.

Dopamine Receptor D1 These receptors belong to the D1-like receptor family and are the most abundant subtypes in the brain [12, 13]. Dopamine receptor D1 (DRD1) concentration is highest in the striatum, cerebral cortex, olfactory bulb, and to a lesser degree in the hippocampus and amygdala [14]. Previous studies on DRD1 receptor knockout mice, an animal ADHD model, have revealed reduced striatal volume [15], increased motor activity [16],

Table 1 Major study findings on excitatory dopamine D1-like receptor subtypes using animal and human models

Receptor subtype:	Major study findings:
Excitatory dopamine D1 receptor (DRD1) subtype	DRD1 knockout mice (an animal model for ADHD): • Reduced striatal volume [15] • Increased motor activity [16] • Hyperactivity [16–18] • Decreased effects of stimulants [16–18] • Poorer performance in tasks [19] • Loss of hyperactivity in response to stimulants [20] Human studies: • Attention and memory regulation [23] • Significant and positive relationship between one polymorphism and inattentive symptoms [24] • Significant association between two DRD1 polymorphisms and ADHD [25]
Excitatory dopamine D5 receptor (DRD5) subtype	DRD5 knockout mice: • No locomotor change in response to cocaine stimulus [20] Human studies: • Several DRD5 polymorphism associations with ADHD [31–40] • Some authors found no significant association [41, 42]

Table 2 Major study findings on inhibitory D2-like dopamine receptor subtypes using animal and human models

Receptor subtype:	Major study findings:
Inhibitory dopamine D2 receptor (DRD2) subtype	DRD2 knockout mice: • Locomotor hyperactivity [48] • Extremely increased reward behavior [48] Spontaneously hypertensive rat (an animal model of ADHD): • Implicated in hyperactivity and impulsivity [43•] Human studies: • Implicated in locomotion modulation [51, 52] • Used as a drug target for neuropsychiatric disorders [53, 54] • Association with impulsive behaviors [55] • Association with executive functioning, spatial working memory, and planning [56]
Inhibitory dopamine D3 receptor (DRD3) subtype	DRD3 knockout mice: • No relevant data Human studies: • 4 polymorphisms associated with prefrontal neurocognition [62] • High concentration in the striatum [58] • Prefrontal cortex regulation [62] • Association with addictive behaviors and impulsive personality [63] • Inhibitory effects on locomotion [64, 65] • Inhibitory effects on motivation [65] • Association with emotion regulation [65] • Association with ADHD [66] • Relationship with hyperactivity and impulsivity [67]
Inhibitory dopamine D4 receptor (DRD4) subtype	DRD4 knockout mice: • Decreased novelty seeking [73] • Coordinated movement dysregulation [75] • Irregular response to stimulants [75] Human studies: • A 7-repeat allele of variable number tandem repeats (VNTR) found to be a significant association as an ADHD risk factor [41, 76–101] • 7-repeat allele associated with lower level of ADHD impairment [76] • 7-repeat allele carriers reportedly have thinner cortex in certain brain regions [117] • 7-repeat allele associated with behavioral aspects of ADHD rather than cognitive changes [118, 119]

hyperactivity, decreased effects of cocaine and amphetamine [16–18], poorer performance and slower learning ability in the Morris water maze task [19], and modest basal hyperactivity [20]. DRD1 knockout mice were also shown to lose hyperactivity in response to stimulant drugs [20]. DRD1 is known to be preferentially expressed in the prefrontal cortex and striatum [21, 22]. Prefrontal cortex DRD1 has also been linked to attention and memory regulation [23]. Previous studies have revealed that prefrontal cortex dysfunction could contribute to the difficulties seen in ADHD, and subjects with impaired prefrontal cortices perform ADHD-like behavior [21, 22]. Through four biallelic DRD1 polymorphisms, D1P.5, D1P.6 9, D1.1 9, and D1.7, researchers revealed significant and positive relationships between D1P.6 and the inattentive symptoms of ADHD in human studies [24]. This study found no link between the other three variations, nor did they reveal any association with the hyperactive or impulsive symptoms of ADHD [24]. A later case–control study revealed a significant association between ADHD and two DRD1 single nucleotide polymorphisms [25]. These findings suggest that specific symptoms of ADHD, such as hyperactivity and inattentiveness, may be related to dopaminergic dysfunction at the receptor subtype level. This allows a new avenue for potential drug targets to be explored. Pharmacotherapy that modulates specific DAR may be able to treat specific clinical presentations of ADHD.

Dopamine Receptor D5 These receptors also belong to the D1-like receptor family [26]. While dopamine receptor D5 (DRD5) has less expression in the brain compared to DRD1, it has a higher affinity for dopamine than DRD1 [20]. Unlike in DRD1 knockout mice, DRD5 knockout mice revealed no change in acute locomotion in response to stimulants [20]. DRD5 receptors have been shown to be expressed in the supraoptic nuclei and the paraventricular nuclei in humans [27]. DRD5 receptors have been implicated in the inhibition of locomotion, as opposed to the similar DRD1 which may facilitate movement [28]. Studies have also associated DRD5 receptors with hypothalamic modulation [27, 28] and forms of motor control [29].

Human studies have revealed the association between ADHD and a polymorphic dinucleotide repeat for the

DRD5 gene, comprising 12 alleles ranging from 134 to 156 base pairs in length [30]. A meta-analysis on the association between ADHD and the nucleotide repeats in 136, 138, 146, 148, 149, and 150 base pairs revealed that the 136 and 148 single nucleotide polymorphisms showed an association with ADHD [31–40]. The dinucleotide repeat of the 148 base pair allele was shown to be a risk factor for ADHD symptoms into adolescence consistent with previous studies [39, 40], while one meta-analysis revealed the 136 base pair allele to potentially work as a protective factor against ADHD [40]. Among individuals with ADHD, the 148 base pair allele was associated with persistent ADHD symptoms into adolescence [39], suggesting that allele variation may influence the clinical outcome of this disorder. A significant association was found between ADHD and base pairs shorter than or equal to 148, while no association was found between ADHD and base pairs longer than 148 [40]. However, these results are not reproducible across multiple studies and others find no significant association with DRD5 polymorphisms [41, 42]. More research is needed to assess the functional implications of these allele variations.

Dopamine Receptor D2 These receptors belong to the D2-like receptor family and are implicated in planning and working memory [43•]. Notably, they have also been studied for possible association with alcoholism and other behavioral disorders [44]. The dopamine receptor D2 (DRD2) is highly distributed throughout the brain with the highest expression in the neostriatum, olfactory tubercle, substantia nigra, ventral tegmental area, and nucleus accumbens as per autoradiography [45] and in situ hybridization [46, 47]. DRD2 A1 allele carriers show significantly lowered glucose metabolism in putamen, temporal, frontal, central, prefrontal, orbital, and occipitotemporal cortices on positron emission tomography (PET) examination with deoxyglucose [47]. In an experimental mouse model of ADHD with a deleted DRD2 polymorphism, hyperactivity in locomotion and extremely increased reward behavior were reported [48]. Through use of spontaneously hypertensive rats, a rat model of ADHD, hyperactivity, and impulsivity was observed along with an increase in DRD2 expression in the substantia nigra and striatum [43•]. Moreover, a meta-analysis supported the association of impulsive–addictive–compulsive behavior with DRD2 [48].

DRD2 is a key receptor in humans that has been widely studied and implicated in the pathogenesis of a variety of other neuropsychiatric disorders. DRD2 signaling is known to modulate locomotion [51, 52] and is utilized as a drug target for neuropsychiatric disorders [53, 54]. DRD2 has also been associated with impulsive behaviors associated with ADHD, such as polysubstance abuse and disinhibition [55]. Previous human studies have also made an association between DRD2 and executive functioning, such as spatial working memory and planning [56], which are also impaired in ADHD.

Dopamine Receptor D3 These receptors belong to the D2-like receptor family [57]. Dopamine receptor D3 (DRD3) are concentrated in striatal regions of the brain and are associated with the limbic system [58]. At the subcellular level, some of the DRD3 receptors are localized in the presynaptic terminal, acting as auto-modulators that regulate neuronal firing and DA synthesis and release [59]. DRD3 receptors are also expressed in mesolimbic brain regions such as the nucleus accumbens, contributing to reward processes, addictive behaviors [60], and incentive-based learning [61].

A human study that examined 4 genetic polymorphisms revealed DRD3 to be integral in dopamine-related prefrontal neurocognition regulated by DRD3 [62]. Dysregulation in this brain region has been associated with addictive behaviors and impulsive personality, both of which are key features of ADHD in adults [63]. DRD3 receptor activity has also been shown to play an inhibitory effect on motor response and locomotion through ventral striatum expression [64, 65], motivation, and emotion regulation through limbic system expression [65]. Guan et al. suggested a distinct significant association of DRD3 with ADHD [66], and a later study indicated the relationship of DRD3 with the manifestation of hyperactive and impulsive symptoms of ADHD [67].

Dopamine D4 These receptors belong to the D2-like inhibitory receptor family. Dopamine D4 (DRD4) receptors are widely expressed in the brain, especially in the hippocampus, frontal cortex, entorhinal cortex, caudate putamen, nucleus accumbens, olfactory tubercle, cerebellum, supraoptic nucleus, and substantia nigra pars compacta [68]. D4 receptors are also distributed both on the periphery of the cell body [69] and in postsynaptic dendritic shafts and spines in the mammalian striatum [70].

The DRD4 subtype modulates several circuits throughout the central nervous system. For example, it modulates the corticostriatal pathway by changing the activity of glutamate receptors, phospholipid methylation, and kinetics of ion channels, which all play a role in the synaptic strength and modulation of neuronal firing activity that is postulated to be impaired in ADHD [71, 72]. Like DRD2, DRD4 has been associated with other neuropsychiatric disorders. DRD4 knockout mice were shown to have a decrease in novelty seeking [73]. This may be related to the behaviors associated with ADHD, as novelty seeking was self-reported to be increased in ADHD patients [74]. Another study using the DRD4 knockout mice model proposed that DRD4 is responsible, in part, for coordinated movements and drug-stimulated behaviors [75].

Human studies have linked a 7-repeat allele of a variable number tandem repeat (VNTR) of the coding region in the DRD4 gene with ADHD, suggesting that this genotype is associated with a lower level of ADHD impairment and symptomatology [76]. The VNTR polymorphisms seen within the DRD4 nucleotide sequence (two, three, four, six, and eight-repeat allele) were not associated with ADHD [41, 76–101]. However, the seven-repeat allele was found to be significantly associated as an independent risk factor for ADHD [39, 76, 78–82, 87–116]. Additionally, DRD4 seven-repeat allele carriers have been documented to have a thinner cortex in the orbitofrontal/inferior prefrontal and posterior parietal areas, along with a unique trajectory of cortical development and right parietal cortical thickening during adolescence, like the findings in ADHD [117]. Non-carrier ADHD patients (without a seven-repeat allele) were shown to have longer reaction time, which suggests that this specific allele may be associated with behavioral aspects of ADHD but not with cognitive changes [118, 119].

Conclusion

Currently approved ADHD medications, such as methylphenidate and mixed amphetamine salts, are known to affect DA signaling in the brain in a non-specific manner. Dopamine and dopaminergic receptor dysfunction in the brain have been identified in a host of neuropsychiatric diseases including ADHD. While dopamine dysregulation is thought to be integral to the process of ADHD, there remains a gap in the research for targeting specific receptors when given a specific presentation of ADHD. This is to say, although we understand that there are two general classes of DAR—stimulatory and inhibitory—there is a lack of research on how targeted pharmacotherapy may be able to modulate behaviors in various presentations of ADHD. More research is needed to determine if specific receptors are implicated in the various behavioral presentations of ADHD. More knowledge on dopamine receptor functionality in the pathophysiology of ADHD may allow for the development of receptor-specific pharmacotherapy with better treatment outcomes and side effect profiles.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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