The Role Of The Dopamine Transporter Gene (DAT1) In Dopamine Dysregulation In Attention-Deficit/Hyperactivity Disorder (ADHD)

ABSTRACT

Background
Attention-deficit/hyperactivity disorder (ADHD) is a widespread neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity, and impulsivity. The dopamine transporter gene (DAT1) plays a significant role in dopamine dysregulation. DAT1 encodes the dopamine transporter protein, which regulates the reuptake of dopamine in the brain.

Objective
This article explores the role of the DAT1 gene and its genetic variations in ADHD pathophysiology. Additionally, this review explores patient responses to treatments like methylphenidate (MPH), and its effects on cognitive functioning.

Methods
This review article used sources from search engines such as PubMed and the National Institute of Health. Keywords searched included ADHD, DAT1, and dopamine. This article excludes sources not written in English.

Results
Results show that specific DAT1 variations are linked to symptoms of ADHD such as inattention, impulsivity, and medical treatments. Furthermore, DAT1 variations work with environmental factors and patterns in DNA methylation to influence emotional and behavioral traits in individuals with ADHD.

Conclusion
This information supports the role of the DAT1 gene in ADHD and pushes for more personalized medical approaches for treating the disorder and detecting ADHD early. Future studies should focus on interactions between the DAT1 gene and its environment and pharmacological advancements to improve ADHD treatments.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a widespread neurodevelopmental disorder that affects millions of children and adults worldwide[1]. It is characterized by symptoms of inattention, hyperactivity, and impulsivity [1]. While the exact causes of ADHD are not fully understood, research has linked the disorder to neurobiological factors like dopamine dysregulation [2]. Dopamine is a neurotransmitter that plays an important role in regulating executive functions like attention and motivation, which are impaired in individuals with ADHD [3]. Many genetic factors influence dopamine dysregulation in ADHD, but the dopamine transporter gene (DAT1) was found to be a key factor due to its involvement in the structure of ADHD in the brain [4].

The DAT1 gene codes for the dopamine transporter protein, which is responsible for the reuptake of dopamine from the synaptic cleft back into the presynaptic neuron [5]. This process is crucial because of how important it is to maintain the balance of dopamine levels in the brain, especially in areas that are mainly associated with cognitive function, such as the prefrontal cortex [6]. Variations or polymorphisms in the DAT1 gene, especially the 40-base pair variable number tandem repeat (VNTR) polymorphism, have been shown to impact the effectiveness of the reuptake of dopamine [7]. These genetic variations can either lead to an overactive or underactive dopamine system, which can result in defects in cognitive and behavioral functioning that ultimately could be considered symptoms of ADHD [8].

This review explores the role of the DAT1 gene in the dysregulation of dopamine associated with ADHD, with a specific focus on genetic variations, their influence on patient response to pharmaceutical treatments, and their impact on cognitive performance in patients. Research has shown that individuals with certain polymorphisms of the DAT1 gene could exhibit a variety of responses to medications such as methylphenidate (MPH), which works by inhibiting the reuptake of dopamine to increase the amount of dopamine that is available in the brain [9]. Additionally, the relationship between the DAT1 variations and cognitive functions such as spatial working memory (SWM), attention, and impulsivity has been thoroughly researched, which ultimately supports the existing information about the mechanisms by which these genetic factors contribute to ADHD symptoms [10].

This review will examine all previous research on the relationship between DAT1 gene variations, medication response, and cognitive functioning to provide a detailed understanding of how all of these factors contribute to ADHD symptomatology. Furthermore, it will utilize these findings to suggest potential personalized medical approaches to ADHD treatment and highlight the need for further research to reveal the complexities behind the interactions between genes and their environment that are associated with ADHD.

METHODS

To obtain the reviewed articles, PubMed and Google Scholar were searched using keywords including ADHD, DAT1, dopamine, dopamine dysregulation, and polymorphism. Articles published within the last 25 years were limited to those selected based on their relevance to the research question. This review article excludes articles not written in English.

RESULTS

Albrecht et. al showed that children with ADHD exhibited lower Cue-P3 amplitudes, meaning that they exhibited decreased attention or ability to process cues [11]. This can occur when patients are unmotivated or tired, both of which are factors that can affect an individual with ADHD [11]. These children also exhibited lower CNV (contingent negative variation) amplitudes, signifying that they had reduced activity in the brain when it came to anticipating a cue [11]. Lastly, they exhibited lower Nogo-P3 amplitudes, meaning that in terms of "Go/NoGo" signals, there are problems when responding [11]. It was also found that children with the 7-repeat (7R) allele showed overall reduced cognitive functioning, coupled with lower Cue-P3 and CNV amplitudes; however, their Nogo-P3 amplitude was not impacted by the allele [11]. On the other hand, children with the DAT1 10-6 haplotype showed normal cognitive functioning and their Cue-P3 and CNV amplitudes were normal, but the Nogo-P3 amplitudes increased [11]. There was found to be no relationship between genotype and ADHD symptomatology [11].

Shang and Gau looked at how variations in the DAT1 gene might be related to ADHD and the ability to perform tasks from memory [12]. Three regions of the gene, called haplotype blocks, were identified, but none of them showed a strong relationship to ADHD overall [12]. Two specific genetic variations of the DAT1 gene, rs27048 and rs429699, showed some connection, but it wasn't strong enough to be considered significant for the experiment [12]. When these two variations were combined into a haplotype block, however, there was a strong connection to the inattentive subtype of ADHD [12]. Additionally, a haplotype in one gene region was also tied to making more errors in cognitive functioning, and this stayed significant after further considerable testing [12]. Lastly, similar results were found when only looking at male participants [12].

Jeong et. al found no association between the 25-item Wender Utah Rating Scale (WURS-25) score and any of the DAT1 genetic markers [13]. On this scale, a score of 46 or higher suggests that an individual has a stronger chance of being diagnosed with ADHD in their childhood [14]. With a score lower than 46, it is unlikely that childhood ADHD will be present [14]. It was found that the trait of mood instability was significantly linked to the rs2937639 variation in male participants [13]. This finding was also supported by analyzing haplotype blocks with nearby variations on the gene, which showed strong associations with the mood instability trait as well [13].

Hasler et. al found significant differences in gene expression when specifically focusing on the DAT1 40-bp VNTR, DRD4 48-bp VNTR, and DRD2-141C Ins/del polymorphisms [15]. The DRD2-141C Ins/del polymorphism refers to a specific variation of the dopamine receptor gene D2, which plays a significant role in dopamine signaling in the brain [15]. This polymorphism showed no significant differences when comparing individuals with ADHD and the control [15]. The DAT1 9.5-repeat (9.5R) allele was not seen as much in individuals with ADHD and it was also linked to lower scores for impulsivity and anger [15]. However, after multiple tests, these findings were not replicated enough to be significant [15]. The DRD4 6-repeat (6R) allele was more common in individuals with ADHD because specific genotypes like the 4-repeat (4R) or 6R allele were associated with higher impulsivity scores and lower anger scores [15]. Additionally, individuals who suffered from physical abuse either in their childhood or adulthood with the 6R allele showed higher impulsivity scores compared to those without the 6R allele [15].

Loo et. al showed that the DAT1 allele influenced both cognitive functioning and electroencephalogram (EEG) responses to medication in children with ADHD [16]. Children with two copies of the 10-repeat allele (10R) showed decreased ability to complete a task compared to those with one or more copies of the 9-repeat (9R) allele [16]. Additionally, children with the 10R allele showed changes in EEG activity after administering medication. They had increased β power in the central and parietal regions of the brain, which indicates increased levels of focus and brain activity [16]. They also had decreased θ power in the frontal region of the brain, meaning they were less relaxed or drowsy [16]. Lastly, they also showed lower θ/β ratios, which measure attention and alertness [16]. In contrast, children who possessed the 9R allele showed the opposite pattern, which suggests that based on their DAT1 allele type, children can exhibit different responses to medication [16].

Bellgrove et. al explored the possibility that the DAT1 genotype potentially influences left-sided or right-sided inattention in children with ADHD [17]. Children with the high-risk DAT1 genotype, meaning they carry two copies of the 10R allele, exhibited a rightward spatial bias and left-sided inattention, while those with the low-risk genotype showed a leftward spatial bias and right-sided inattention [17]. Additionally, children who carried the high-risk DAT1 genotype significantly improved their ADHD symptoms after being treated with methylphenidate (MPH), specifically with hyperactivity and impulsivity [17]. There was no effect on attentional cue processing [17]. These findings suggest that the DAT1 genotype–both high-risk and low-risk–plays a role in both attentional cue processing and response to MPH in individuals with ADHD [17].

Marzilli et. al looked into how children's ADHD symptoms could potentially be associated with DNA methylation at various CpG (cytosine-phosphate-guanine) sites, specifically M1, M2, M6, and M3 [18]. DNA methylation at the M1 site was strongly connected to ADHD symptoms, while methylation at the M2 and M6 were weakly correlated [18]. Both maternal and paternal

environmental factors, including childhood stress, also impacted children's DNA methylation levels, but they were additionally regulated by the child's DAT1 genotype [18]. Maternal factors, in particular, showed stronger connections with DNA methylation in children with the 10/10 genotype, while paternal factors showed a stronger connection in children with the 9/x genotype [18]. These findings suggest that both genetic and environmental factors play a role in the DNA methylation patterns associated with ADHD and emotional/behavioral dysregulation in children [18].

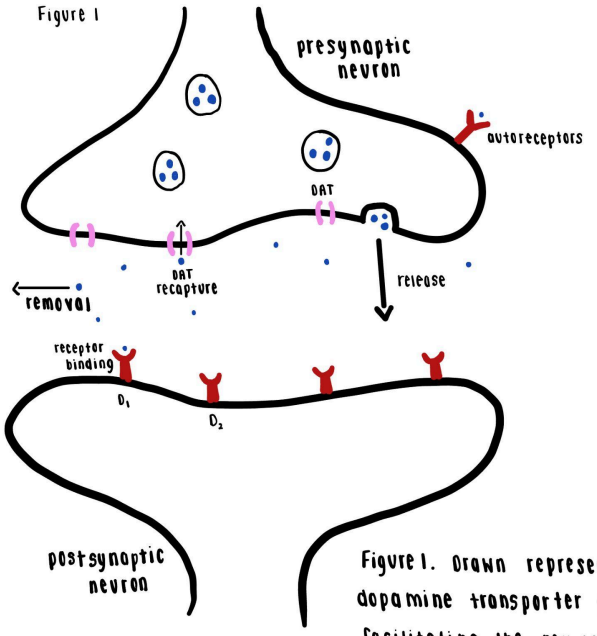

Figure 1. Drawn representation of the dopamine transporter gene (DAT1) facilitating the reuptake of dopamine from the synaptic cleft back into the presynaptic neuron.

DISCUSSION

This review article provides essential information when it comes to the complex and nuanced relationship between the DAT1 gene polymorphism and the behavioral and cognitive functioning of individuals with ADHD. These findings align with the increasing amount of research that suggests that genetic factors play a crucial role in the development of ADHD symptoms in children and adults [18]. Additionally, the data in this article continues to support the idea that these genetic factors influence a variety of emotions and behaviors, particularly impulsivity, anger, hyperactivity, and inattention, all of which are central traits associated with ADHD [15].

The DAT1 Gene And Its Role In Emotional And Behavioral Functioning

Hasler et al. focus specifically on the role of the DAT1 polymorphism in ADHD symptoms, specifically impulsivity and inattention [15]. They found that variations in the DAT1 gene influenced the expression of impulsivity and anger, which were notably different between ADHD patients and controls [15]. This potentially implies that the DAT1 gene may impact not only the most common traits found in ADHD but also the emotional and behavioral aspects of the disorder [15].

Previous research suggests that the DAT1 gene does influence the regulation of dopamine, a neurotransmitter that is critical in the role of attention and emotional regulation [5]. Specific alleles of the DAT1 gene, such as the 9.5R allele, were associated with lower impulsivity and anger scores, supporting the idea that certain genetic polymorphisms could support some of the emotional dysregulation associated with ADHD [15]. This information helps to understand why it is important to view ADHD as a multifaceted disorder influenced by both genetic factors and emotional/behavioral factors.

The Neuropsychological Effects Of The DAT1 Polymorphism

Bellgrove et al. looked into additional information that could support the hypothesis that the DAT1 gene influences specific cognitive functions, particularly inattention and impulsivity [17]. It was found that individuals with certain DAT1 genotypes, specifically those with the 10R allele, exhibited higher trait scores of inattention [17]. These results support the idea that the DAT1 gene potentially influences cognitive processes such as attention, specifically in terms of spatial working memory (SWM) [17]. In this study, left-sided inattention was linked to the 10R allele, which further reinforces the idea that neuropsychological and cognitive performance is connected to specific DAT1 genetic polymorphisms [17].

There was also information supporting the possibility of a relationship between the DAT1 polymorphism and patient response to methylphenidate (MPH), which is a common ADHD medication [17]. The improved response to MPH in individuals with left-sided inattention, particularly those who possessed the 10R allele, suggests that genetic variations can influence not only the development of ADHD but also the effectiveness of various treatments for the disorder [17]. This result emphasizes the importance of accounting for genetic factors when considering treatment plans for individuals with ADHD.

Implications For Preventive Programs

Marzilli et. al explores the idea that emotional and behavioral functioning in children with ADHD is not only determined by observable symptoms but can also be determined by underlying genetic factors such as DNA methylation [18]. This is important to consider when designing preventive programs for ADHD. With these programs, the rate of early interventions

will increase and ADHD treatment can be approached in a more preventive way. To implement these programs, however, it's crucial to be able to understand the role of the DAT1 gene in regulating the traits and symptoms associated with ADHD.

The relationship between various DAT1 genotypes and patient response to MPH suggests that preventive programs could potentially benefit from using genetic information to predict the outcome of the treatment [17]. With the help of these programs, healthcare professionals can identify children at risk of developing ADHD or those who have a decreased response to certain ADHD treatments, allowing for early intervention or the development of alternative treatment approaches that might work better.

Relevance And Future Directions

Jeong et. al explores the emotional effects of ADHD which is relevant because of its potential to contribute to a deeper and more nuanced understanding of ADHD and its underlying genetic factors [13]. By focusing on the DAT1 polymorphism and its impact on emotional and behavioral traits found in children and adults with ADHD, this research highlights the complex nature of ADHD and acknowledges that a multifaceted approach to treatment and prevention is necessary in the future [13]. Typically, ADHD is often associated with a variety of other conditions, such as mood disorders [19]. To incorporate the genetic foundation of the emotional dysregulation that is associated with ADHD, there could be numerous benefits when it comes to treating the other conditions as well.

Future research on this topic should try to replicate these findings in larger numbers to confirm the presented data and expand on the DAT1 polymorphism and emotional/behavioral traits. Longitudinal studies could also be conducted to help clarify the role of the various DAT1 genetic variations in the development of ADHD symptoms. Furthermore, future research should also look into the relationship between genetic factors and environmental influences, such as childhood stress or family dynamics, specifically maternal and paternal influences.

Lastly, more research on the pharmacogenetic aspects of ADHD treatment is necessary. Bellgrove et al. emphasize that genetic factors like the DAT1 polymorphism can significantly influence patient response to MPH [17]. If these relationships are better understood, more effective and personalized treatments for individuals with ADHD can be developed.

Conclusion

This review covers the role of the DAT1 gene in ADHD pathophysiology, specifically its role in dopamine dysregulation, emotional and behavioral traits, and patient response to medical treatments. Variations in the DAT1 gene, like the 10-repeat allele, are linked to symptoms of ADHD such as inattention and impulsivity. These results support the importance of more personalized treatments for ADHD to increase the rates of early diagnosis.

Additionally, this information emphasizes the relationship between genes and their environment, and how it all affects ADHD symptomatology. Future research on this topic should explore those gene-environment relationships and look more into potential treatments for ADHD. Potentially using patients' genetic profiles could lead to more personalized approaches to treatment.

All in all, utilizing genetic information about ADHD can only improve all aspects of ADHD treatment and diagnosis. By continuing to research more on the role of the DAT1 gene in ADHD, every facet of this nuanced disorder can be better understood for future medical research.

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