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Neurobiology of Attention Deficit Hyperactivity Disorder (ADHD): A brief review

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a common condition associated with long-lasting psychosocial functioning difficulties and high psychiatric morbidity. ADHD is a heterogeneous syndrome in its clinical presentation and probably in its aetiology. Nevertheless, it can be understood as a spectrum of multifactorial cognitive, emotional, and behavioural dysfunctions under the influence of genetic and environmental factors, mainly perinatal. For several decades, the dopaminergic dysfunction hypothesis has been one of the possible pathways in the origin of ADHD. Still, other neurotransmission systems also appear to play a role, as evidenced by the recent therapeutic development of noradrenergic agonists in this indication.

Keywords: Attention deficit hyperactivity disorder; Pathophysiology; Biology; Genetic; Risk

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is defined in the DSM-5-TR as one of the neurodevelopmental disorders with the highest prevalence among the child population. It is characterised by the presence of five or more symptoms for people over 17 years of age and six symptoms or more for children under 16, which, according to the present symptomatology, can be distinguished into three modalities: hyperactive, inattentive, or mixed [1]. Psychobehavioral interventions can improve the cardinal symptoms of ADHD, and pharmacological treatments, the most used, are psychostimulants (derivatives of methylphenidate and amphetamines). A combination of attention deficit disorder and cognitive, emotional, and behavioural control difficulties characterises this disorder. Clinically, it manifests as impulsivity, problems anticipating and organising tasks, difficulties maintaining attention, and motor instability of varying degrees. The prevalence calculated from a systematic literature review that includes 102 epidemiological studies from all continents is 5.29% [2]. It is a chronic disorder associated with academic, social, and family repercussions in children whose functional discomfort is still identifiable in more than 60% of the adults involved [3]. ADHD is often associated with psychiatric comorbidity (conduct and opposition disorders, anxiety disorders) and learning difficulties and constitutes a risk factor for substance abuse and dependence [4]. The repercussions on the family circle, school and professional trajectories, and social and health costs are indirect consequences of ADHD [5].

Given the complexity of determining genetic characteristics, these have not been separated according to the types of ADHD that may occur, namely hyperactive, inattentive, or mixed, pending future research to determine if there are genetic differences between each subtype.

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1.1. Potential risk factors

The overrepresentation of ADHD in families of affected individuals is well documented. Twin studies have estimated that the heritability of ADHD is 76%, with the rest of the variation being mainly due to the unshared environment [6]. Heritability includes all additive genetic factors, i.e., the weight of different genes, their mutual interaction, and their interaction with the environment. However, this estimate does not indicate the causes of ADHD. Dimensions such as impulse, inattention, and motor activity are influenced by genetic factors common to the average population and people with ADHD. The environmental factors incriminated in vulnerability to ADHD refer mainly to the perinatal period. Case-control studies show that prenatal tobacco exposure is twice the risk of ADHD in exposed children without the various confounding factors (socioeconomic status, IQ, parental ADHD, alcohol abuse, birth weight...) that fully explain this result [7]. A double study showed that most of the variation in ADHD is related to shared genetic factors, but the association with tobacco exposure remains significant [8]. Other factors involved include prenatal exposure to alcohol and other psychoactive substances, prematurity and low birth weight, maternal stress and nutritional deficiencies during pregnancy, and exposure to polychlorinated biphenyls (PCBs), hexachlorobenzene and lead [9]. ADHD symptoms can also accompany acquired brain damage (traumatic or postencephalitic). Psychosocial factors have also been associated with ADHD (hostile parenting attitudes, maternal depression), but the direction of causality is not established due to multiple confounding factors (e.g., the existence of ADHD in parents may influence their educational style).

1.2. Neurobiological mechanisms

The role of catecholamines in hyperkinetic syndromes in children was highlighted in the 1970s after discovering the therapeutic effect of psychostimulants, the main medication for attention deficit hyperactivity disorder. Therefore, methylphenidate increases the dopamine concentration in the synaptic cleft through the blockade of the dopamine transporter (DAT). Functional imaging data show that this increase in extracellular dopamine is more significant after exposure to an environmental stimulus with a reinforcement value (mathematical test) than after a neutral stimulus [10]. The authors propose that the extracellular increase of dopamine in striatal neurons would decrease their essential random activity and allow corticostriatal afferents linked to the relevant stimuli to be more effective. Successive neuropharmacological studies and the discovery of the therapeutic action of noradrenergic agonists have led to refining the hypothesis of dopaminergic exhaustion involved in the inhibition defect and the abnormalities of the reinforcement system described in ADHD [11]. Through postsynaptic alpha2A receptors located in the dendritic spines of glutamatergic neurons, Noradrenaline increases synaptic responses in the prefrontal network. Noradrenergic molecules such as atomoxetine and guanfacine, in addition to an improvement in attention and working memory capacities through their action in the prefrontal cortex, would facilitate the inhibitory action of the latter in the motor cortex and subcortical regions [12]. As shown in striatum imaging studies, dopamine is expected to increase the relevant signal-to-background ratio in glutamatergic neurons in the prefrontal cortex by activating D1 receptors [13]. All these data suggest a complex neurobiological basis, which goes beyond an exclusive dopaminergic hypothesis (for a critical review of the dopaminergic hypothesis, see [14]) and involves a diversity of molecular targets.

1.3. Molecular genetic studies

This approach examines many DNA markers to determine whether affected members of families most often share certain chromosomal regions with ADHD. The seven genome detection studies conducted in German pairs, multiplex families or genetic isolates show convergent data for specific regions (5p13, 9q22 and 16q23), but none showed a significant statistical union in all samples. However, a meta-analysis of these studies highlighted a vital link for a region of 64 to 83 Mb on chromosome 16 [15]. In ADHD, a mismatch is identified between high heritability and low-risk ratio attributable to genes identified in association studies, particularly those related to the entire genome and other diseases, including aetiology. It is complex. Manolio et al. have published an in-depth discussion of the concept of "lost heritability" and proposals for new genetic study strategies [15].

1.4. Epigenetic mechanisms

In all neuropsychiatric diseases, as more generally in behaviour, the intervention of molecular mechanisms linked to parental genomic imprinting concerning chromatin modifications resulting in gene expression modifications has been foreseen [16]. Preferential transmission of the paternal allele has been demonstrated for the SNAP25 gene encoding a protein involved in neurotransmitter release [17]. The mouse model of invalidation of the homologous murine gene SNAP25 has phenotypic traits reminiscent of the disease. Epigenetic modifications related to chromatin remodelling have been identified in certain neuropsychiatric diseases and addicts. They have not been documented to date in ADHD. This line of research is a promising avenue, as Mill and Petronis point out [16].

1.5. Pharmacogenetic studies

Studies of genetic factors involved in individual variations in drug tolerance and efficacy have focused primarily on polymorphisms in dopaminergic genes. Thus, the VNTR (tandem repeat variable number) 3'UTR of the DAT1 gene (SLC6A3) was the first polymorphism involved in the efficacy of methylphenidate [18]. Subsequent studies have not replicated all these results, probably due to the great diversity of methods employed. A meta-analysis of pharmacogenetic studies that have studied this polymorphism found an association between genotype 10-R/10-R and a lower response to treatment with an OR (odds ratio) of 0.46 [18]. Although less studied, other polymorphisms, such as VNTR DRD4*7 (dopamine D4 receptor), alone or in interaction with the L variant of the serotonin transporter promoter region (5-HTTLPR), have been associated with the response to methylphenidate [19].

1.6. Gene-environment interactions

A major difficulty in studying genes involved in behavioural disorders comes from the interaction of these genes with the environment. For example, the risk of ADHD for children exposed to nicotine in the womb is higher if the child has inherited the 10-repeat allele of DAT1 [20]. Nicotine, in prenatal exposure, would interact with the genotype at the level of at least three loci (CHRNA4, nicotinic cholinergic receptor alpha 4, DAT1, and DRD4) as proposed by the synaptic model of Todd and Neuman [21]. In addition, nicotine would promote dopamine release in the prefrontal cortex. During cortical development, dopamine has morphogenetic effects mediated by the dopaminergic receptor D4, inducing changes in neuronal maturation in the foetus.

2. Imaging studies

2.1. Structural imaging

Morphometric studies conducted in children with ADHD show more generalized alterations than expected, according to pathophysiological data related to frontostriatal circuits [22]. Reductions in brain volume (the different lobes, the caudate nucleus) and cerebellum have been demonstrated in numerous studies. A meta-analysis based on 22 individual studies confirmed these data [23]. Recent studies in a large cohort (223 children with ADHD and 223 control children) have shown a delay in cortical maturation in patients with ADHD, particularly pronounced in the prefrontal cortex. This delay in maturation is estimated at three years: the cortical thickness in ADHD patients of 10.5 years is like that observed in control children of 7.5 years [24]. This study shows the existence of developmental abnormalities of a particular type while there is no demonstrated deviation in cortical maturation. However, there is a very long maturation period (the average time required to reach 50% of the maximum thickness is 7.5 years in controls versus 10.6 years in children with ADHD).

2.2. Functional images

Functional imaging studies have mainly investigated cognitive tasks related to attention control, working memory, and response inhibition. A recent meta-analysis of this work shows a significant activation defect in the left prefrontal cortex, anterior cingulate cortex, right parietal lobe, occipital cortex, and thalamus in subjects with ADHD compared to controls [25]. In general, subjects with ADHD show frontal dysfunctions during tasks involving response inhibition and temporoparietal tasks for those requiring attention. In addition, subjects with ADHD generally have reduced activation of the striatum on functional magnetic resonance imaging and show less activation of a ventral striatum-cingular network during motivational tasks involving reinforcement [25]. The imaging study of the effects of treatment shows, in some cases, normalization of the excess striatal density of DAT, a prominent feature in subjects with ADHD before exposure to psychostimulants, but whose attempts at replication have yielded variable results. Functional imaging, along with the study of genotypes, shows that certain alleles of vulnerability to ADHD are involved in performance on working memory tests and activation patterns in healthy subjects. Therefore, a decrease in activity in the anterior cingulate cortex was found in functional nuclear magnetic resonance imaging in healthy subjects, depending on the number of methylated alleles of the gene encoding the enzyme responsible for the degradation of catecholamines (Val158Met polymorphism of the COMT gene) [26]. Similar results were observed for the 10-R allele of DAT1 [26]. Structural and functional imaging data open interesting avenues for exploring new etiopathogenic mechanisms of ADHD (e.g., the possible role of neurotrophins in the period of cortical maturation).

3. Conclusion

ADHD is a complex disorder with multiple contributing factors. While genetic factors have been shown to play a significant role in the development of ADHD, current research suggests that it is not caused by a single gene but rather by the combined effects of multiple genes, each associated with low risk. These genes interact with each other and with

environmental factors to produce the clinical expression of the disorder. Recent advances in neurobiological research have led to the identification of several polymorphisms linked to ADHD vulnerability genes. Collaborative networks and improved techniques have made it possible to collect morphological and functional data that can be correlated with these polymorphisms. This data is essential to better understand the heterogeneity of the disorder and its developmental dimension. Ongoing research into the polymorphisms of ADHD vulnerability genes and the interactions between genes and environmental factors will be necessary to develop more effective treatments for this disorder.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare to have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5-TR. Washington, DC: American Psychiatric Publishing; 2022.

[2] Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry. 2007 Jun;164(6):942-8.

[3] Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M. Adult psychiatric status of hyperactive boys grown up. Am J Psychiatry. 1998 Apr;155(4):493-8.

[4] Mannuzza S, Klein RG, Truong NL, Moulton JL 3rd, Roizen ER, Howell KH, Castellanos FX. Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. Am J Psychiatry. 2008 May;165(5):604-9.

[5] Galéra C, Melchior M, Chastang JF, Bouvard MP, Fombonne E. Childhood and adolescent hyperactivity-inattention symptoms and academic achievement 8 years later: the GAZEL Youth study. Psychol Med. 2009 Nov;39(11):1895-906.

[6] Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005 Jun 1;57(11):1313-23.

[7] Langley K, Rice F, van den Bree MB, Thapar A. Maternal smoking during pregnancy as an environmental risk factor for attention deficit hyperactivity disorder behaviour. A review. Minerva Pediatr. 2005 Dec;57(6):359-71.

[8] Thapar A, Fowler T, Rice F, Scourfield J, van den Bree M, Thomas H, Harold G, Hay D. Maternal smoking during pregnancy and attention deficit hyperactivity disorder symptoms in offspring. Am J Psychiatry. 2003 Nov;160(11):1985-9.

[9] Mick E, Biederman J, Faraone SV, Sayer J, Kleinman S. Case-control study of attention-deficit hyperactivity disorder and maternal smoking, alcohol use, and drug use during pregnancy. J Am Acad Child Adolesc Psychiatry. 2002 Apr;41(4):378-85.

[10] Volkow ND, Wang GJ, Newcorn JH, Fowler JS, Telang F, Solanto MV, Logan J, Wong C, Ma Y, Swanson JM, Schulz K, Pradhan K. Depressed dopamine activity in caudate and preliminary evidence of limbic involvement in adults with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 2007 Aug;64(8):932-40.

[11] Sagvolden T, Johansen EB, Aase H, Russell VA. A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. Behav Brain Sci. 2005 Jun;28(3):397-468.

[12] Easton N, Steward C, Marshall F, Fone K, Marsden C. Effects of guanfacine and d-amphetamine on impulsive choice in spontaneously hypertensive rats. Behav Pharmacol. 2007 Sep;18(5-6):549-63.

[13] Brennan AR, Arnsten AFT. Neuronal mechanisms underlying attention deficit hyperactivity disorder: the influence of arousal on prefrontal cortical function. Ann N Y Acad Sci. 2008 Dec;1129:236-45.

[14] Gonon F. The dopaminergic hypothesis of attention-deficit/hyperactivity disorder needs re-examining. Trends Neurosci. 2009 Jan;32(1):2-8.

[15] Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, Cho JH, Guttmacher AE, Kong A, Kruglyak L, Mardis E, Rotimi CN, Slatkin M, Valle D, Whittemore AS, Boehnke M, Clark AG, Eichler EE, Gibson G, Haines JL, Mackay TF, McCarroll SA, Visscher PM. Finding the missing heritability of complex diseases. Nature. 2009 Oct 8;461(7265):747-53.

[16] Mill J, Petronis A. Molecular studies of major depressive disorder: the epigenetic perspective. Mol Psychiatry. 2007 Sep;12(9):799-814.

[17] Winsberg BG, Comings DE. Association of the dopamine transporter gene (DAT1) with poor methylphenidate response. J Am Acad Child Adolesc Psychiatry. 1999 Dec;38(12):1474-7.

[18] McGough JJ, Smalley SL, McCracken JT, Yang M, Del'Homme M, Lynn DE, Loo S. Pharmacogenetics of methylphenidate response in preschoolers with ADHD. J Am Acad Child Adolesc Psychiatry. 2006 Nov;45(11):1314-22.

[19] Neuman RJ, Lobos E, Reich W, Henderson CA, Sun LW, Todd RD. Prenatal smoking exposure and dopaminergic genotypes interact to cause a severe ADHD subtype. Biol Psychiatry. 2007 Jun 15;61(12):1320-8.

[20] Bush G. Attention-deficit/hyperactivity disorder and attention networks. Neuropsychopharmacology. 2010 Jan;35(1):278-300.

[21] Todd RD, Neuman RJ. Gene-environment interactions in the development of combined type ADHD: evidence for a synapse-based model. Am J Med Genet B Neuropsychiatr Genet. 2007 Oct 5;144B(8):971-5.

[22] Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, Clasen L, Evans A, Giedd J, Rapoport JL. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci U S A. 2007 Dec 4;104(49):19649-54.

[23] Dickstein SG, Bannon K, Castellanos FX, Milham MP. The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. J Child Psychol Psychiatry. 2006 Oct;47(10):1051-62.

[24] Paloyelis Y, Mehta MA, Kuntsi J, Asherson P. Functional MRI in ADHD: a systematic literature review. Expert Rev Neurother. 2007 Oct;7(10):1337-56.

[25] Sagvolden T. Behavioral validation of the spontaneously hypertensive rat (SHR) as an animal model of attention-deficit/hyperactivity disorder (AD/HD). Neurosci Biobehav Rev. 2000 Jan;24(1):31-9. 26.

[26] Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. Biol Psychiatry. 2007 Jun 15;61(12):1361-9.