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Neurobiology of attention deficit hyperactivity disorder (ADHD)

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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.

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Clinical manifestations

ADHD is defined in the DSM-5-TR as one of the neurodevelopmental disorders with the highest prevalence among the child population. It is characterized 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 (American Psychiatric Association, 2022).

Psychobehavioral interventions can improve the cardinal symptoms of ADHD, and pharmacological treatments, the most

used are psychostimulants (derivatives of methylphenidate and amphetamines). This disorder is characterized by a combination of attention deficit disorder and cognitive, emotional, and behavioural control difficulties. Clinically it manifests as impulsivity, problems anticipating and organizing 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% (Polanczyk et al., 2007). 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 (Spencer et al., 2007). 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 (Mannuzza et al., 1993). The repercussions on the family circle, school and professional trajectories, and social and health costs are indirect consequences of ADHD (Galéra et al., 2009; Mannuzza et al., 2008).

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.

Potential risk factors

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 (Faraone & Doyle, 2001). 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 (Langley et al., 2005). A double study showed that most of the variation in ADHD is related to common genetic factors, but the association with tobacco exposure remains significant (Thapar et al., 2003). 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 (Jonathan Mill & Petronis, 2008). 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).

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 (Volkow et al., 2005). 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 (Sagvolden et al., 2005). 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 (Easton et al., 2006). 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 (Brennan & Arnsten, 2008). All these data suggest a complex neurobiological basis, which goes beyond an exclusive dopaminergic hypothesis (for a critical review of the dopaminergic hypothesis, see (Gonon, 2009)) and involves a diversity of molecular targets.

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 (Manolio et al., 2009). 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 (Tsankova et al., 2007).

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 (J. Mill et al., 2004). Preferential transmission of the paternal allele has been demonstrated for the SNAP25 gene encoding a protein involved in neurotransmitter release (Winsberg & Comings, 1999). The mouse model of invalidation of the homologous murine gene SNAP25 has phenotypic traits reminiscent of the disease (Table III). 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 (Jonathan Mill & Petronis, 2008).

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 (McGough et al., 2006). 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 the association between genotype 10-R/10-R and a lower response to treatment with an OR (odds ratio) of 0.46 (95% CI 0, 28-0.76) (Seeger et al., 2001). Although less studied, other polymorphisms, such as VNTR DRD4*7 (dopamine D4 receptor), alone (Neuman et al., 2007) or in interaction with the L variant of the serotonin transporter promoter region (5-HTTLPR) (Todd & Neuman, 2007), have been associated with the response to methylphenidate.

Gene-environment interactions

A major difficulty in studying genes involved in behavioural disorders comes from interacting 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 (Bush, 2010). 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 (Valera et al., 2007). 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 fetus.

Imaging studies

Structural imagery

Morphometric studies conducted in children with ADHD show more generalized alterations than expected according to pathophysiological data related to frontostriatal circuits (Shaw et al., 2007). 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 (Dickstein et al., 2006). 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 (Paloyelis et al., 2007). 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. This study shows the existence of

developmental abnormalities of a particular type since, 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, $p < 1.0 \times 10^{-20}$).

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 (Sagvolden, 2000). 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 (magnetic resonance imaging) and show less activation of a ventral striatum-cingular network during motivational tasks involving reinforcement (Sagvolden, 2000). 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 been 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). Similar results were observed for the 10-R allele of DAT1 (dopamine receptor).

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).

Conclusion

Neurobiological approaches to ADHD point to an etiological heterogeneity of the disorder. While genetic factors play a crucial role, current data support the existence of multiple loci, each associated with low risk but also with additive genetic effects and gene-gene and gene-environment interactions. It is likely that, soon, collaborative networks and improved techniques will make it possible to correlate morphological and functional data with the polymorphisms of ADHD vulnerability genes and to collect data that integrate different levels of clinical expression, as well as the developmental dimension of the disorder.

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