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Growth Factors, Cell Receptors, Intracellular Kinases, and Transcription Factors Associated with Attention Deficit Hyperactivity Disorder (ADHD)

Russo AJ[1]*, Albert Mensah[2] and Judith Bowman[2]

[1]*Visiting Professor, Hartwick College, Oneonta, NY 13820, Research Director, Mensah Research Institute, Warrenville, Illinois, USA.*

[2]*Mensah Research Institute, Warrenville, Illinois, USA.*

***Correspondence:**

Russo AJ, Visiting Professor, Hartwick College, Oneonta, NY 13820, Research Director, Mensah Research Institute, Warrenville, Illinois, USA, Tel: 240-394-0351.

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ABSTRACT

ADHD, or Attention-Deficit/Hyperactivity Disorder, is a neurodevelopmental condition characterized by persistent patterns of inattentiveness, impulsivity, and hyperactivity that often begin in childhood and can continue into adulthood. This review summarizes many of the growth factors, cell receptors, intracellular kinases, and transcription factors associated with the etiology of ADHD.

Keywords

Attention Deficit Hyperactivity Disorder (ADHD), Growth Factors, Cell Receptors, Intracellular Kinases, Transcription Factors, Neurobiology of ADHD.

Growth Factors Associated with ADHD

ADHD, or Attention-Deficit/Hyperactivity Disorder, is a neurodevelopmental condition characterized by persistent patterns of inattentiveness, impulsivity, and hyperactivity that often begin in childhood and can continue into adulthood [1]. Research has explored various factors associated with ADHD, including genetic, environmental, and neurobiological influences. One significant area of interest is the role of growth factors in the development and manifestation of ADHD symptoms.

Studies have investigated the impact of prenatal factors on ADHD, with findings suggesting that restricted fetal growth may lead to insufficient energy supply for organ development, potentially increasing susceptibility to neurodevelopmental issues later in life, including ADHD [2]. Additionally, research has highlighted the association between preterm birth and ADHD, indicating that the risk for ADHD is higher in children born prematurely, with the degree of prematurity correlating with an increased risk of developing ADHD symptoms [3].

Furthermore, investigations into the role of growth factors such as Insulin-like Growth Factor-1 (IGF-1) have been conducted. IGF-1, known for its role in mediating the effects of growth hormone and supporting fetal, childhood, and adolescent development, has been linked to ADHD [4]. The presence of IGF-1 in the context of ADHD suggests a potential association between growth factors and the neurobiological underpinnings of the disorder.

Moreover, environmental influences, including exposure to toxic substances during early development and fetal adaptations to stress, have been proposed as contributors to dopamine deficits, which are implicated in the etiology of ADHD [5]. These environmental factors may interact with genetic predispositions, affecting dopamine neurons and potentially influencing the development of ADHD symptoms.

In addition to prenatal influences, postnatal factors such as physical exercise have been explored for their potential impact on neural growth and development, with the aim of altering the trajectory of ADHD [6]. Studies have suggested that environmental interventions, including physical activity, could enhance neural development, leading to long-term effects on ADHD symptoms.

Neurotrophic factors, which play crucial roles in neuronal growth and survival, have also been implicated in the pathogenesis of

ADHD [7]. Brain-derived neurotrophic factor, insulin-like growth factor 2, and other growth factors have been identified as potential contributors to the underlying mechanisms of ADHD and related neurodevelopmental conditions.

Overall, the research on growth factors associated with ADHD underscores the complex interplay between genetic, environmental, and neurobiological factors in the development and manifestation of the disorder. Understanding how factors such as prenatal influences, neurotrophic factors, and environmental interventions impact ADHD can provide valuable insights for developing targeted interventions and treatments for individuals affected by the condition.

Cell Receptors Associated with ADHD

ADHD has been extensively studied in relation to various cell receptors. Research has shown that norepinephrine and dopamine play crucial roles in enhancing prefrontal cortical (PFC) function through actions at postsynaptic α2A-adrenoceptors and dopamine D1-receptors, respectively [8]. The dopamine D4 receptor has been highlighted as particularly significant, with gene variants associated with ADHD mediating a blunted response to norepinephrine and dopamine, key neurotransmitters in ADHD pathophysiology [9]. Furthermore, glutamate receptors have also been implicated in ADHD, with genome-wide and candidate gene association studies suggesting their involvement in the disorder [10].

Studies have identified numerous genes linked to ADHD, including those encoding enzymes of neurotransmitter metabolism, transporters, and receptors [11]. The catecholamine neurotransmitter system, which signals through G protein-coupled receptors (GPCRs), has been identified as a critical factor in ADHD development, with dopamine and noradrenaline systems being primary targets for ADHD medications [12]. Additionally, serotonin receptors, such as HTR1B, serotonin transporter (5-HTT), and synaptosomal-associated protein 5 (SNAP-25), have shown associations with ADHD [13]. Decreased Serum Cu/Zn SOD (Superoxide Dismutase) associated with high copper has been linked to ADHD [14].

Genetic studies have also focused on dopaminergic receptors and transporters, such as DRD4, DRD5, and DAT1, due to their role in modulating the dopaminergic system, which is targeted by stimulant drugs used in ADHD treatment [15]. Moreover, the α2A-adrenergic receptor agonist guanfacine extended release has emerged as a non-stimulant treatment option in Europe, shedding light on the roles of catecholamine receptors in ADHD pathophysiology [16]. Additionally, endosomal Na+/H+ exchangers have been linked to ADHD, autism, and other neurological conditions, suggesting a potential connection between these cellular mechanisms and ADHD [17].

The serotonin 5-HT1B receptor gene has been implicated in ADHD development, with altered expression potentially leading to disturbances in the central nervous system, contributing to ADHD pathogenesis [18]. PET scanning studies have revealed decreased levels of the dopamine D1 receptor in individuals with ADHD, particularly in brain regions associated with hyperactive behavior [19]. Furthermore, research in animal models has suggested that deficiencies in parvalbumin interneurons in cortical regions may lead to diminished GABA activity and perturbations in dopamine activity, potentially contributing to ADHD symptoms [20].

The potential targets and action mechanisms of gastrodin in ADHD treatment have been explored, with pathways such as neuroactive ligand-receptor interactions, cholinergic synapses, and dopaminergic synapses identified as core pathways for gastrodin's effects in ADHD [21]. Polymorphisms in dopamine receptors, such as DRD4, have been associated with ADHD, affecting receptor binding and potentially influencing ADHD susceptibility [22]. Moreover, rare copy number variations in genes interacting with metabotropic glutamate receptors have been linked to neurodevelopmental disorders, including ADHD [23].

The serotonergic system, particularly the 5-HT1B receptor gene, has been proposed as a potential susceptibility locus for ADHD, further highlighting the complex interplay of neurotransmitter systems in the disorder [24]. Molecular genetic studies have successfully identified genetic variants associated with ADHD subtypes, shedding light on the genetic underpinnings of the disorder [25]. Multivariate analyses of genes related to dopamine, serotonin, and norepinephrine have provided insights into the genetic associations with ADHD, oppositional defiant disorder, and conduct disorder [26].

In conclusion, ADHD is a multifaceted disorder influenced by a complex interplay of genetic, neurobiological, and cellular factors. The involvement of various cell receptors, neurotransmitters, and genetic variants underscores the intricate nature of ADHD pathophysiology. Understanding the roles of cell receptors associated with ADHD is crucial for developing targeted interventions and personalized treatment approaches for individuals with this disorder.

Intracellular Kinases Associated with ADHD

Several intracellular kinases have been implicated in the pathophysiology of ADHD, shedding light on potential therapeutic targets. One key molecule of interest is mTOR, a serine/threonine kinase crucial for regulating protein synthesis and cell growth, which has been associated with neurological disorders including autism and ADHD [27]. Additionally, GIT1, a multifunctional signaling adaptor, has been linked to ADHD, with studies reporting an association between GIT1 and ADHD in humans as well as ADHD-like behaviors in mice [28,29]. The involvement of GIT1 in ADHD underscores the significance of intracellular signaling pathways in the disorder.

Moreover, disruptions in NMDA receptor transmission have been implicated in driving behavioral pathology in ADHD, with proteins like calcium/calmodulin-dependent protein kinase II (CaMKII) identified as key players in this pathway [30]. The dysregulation of CREB signaling by a kinase-independent PI3Kγ-

PDE4D interaction in the noradrenergic neurons of the locus coeruleus has also been highlighted as a contributing factor to the ADHD phenotype, offering new insights for mechanistic and therapeutic research in ADHD [31]. These findings emphasize the intricate interplay of various kinases and signaling pathways in the manifestation of ADHD symptoms.

Furthermore, the role of brain-derived neurotrophic factor (BDNF) in ADHD pathogenesis has garnered attention, with studies indicating a pathophysiological role of BDNF in the disorder [32-34]. The BDNF/TrkB signaling pathway has been implicated in dopamine vesicle circulation and ADHD pathogenesis, suggesting a potential avenue for therapeutic interventions [33]. Additionally, the recruitment of PI3K to the membrane surface by the CADM1 molecule has been proposed to play a crucial role in affecting upstream signaling pathways involved in ADHD, further highlighting the intricate molecular mechanisms at play [35]. In addition, our lab has found high levels of Protein Kinase B (Akt) concentration in ADHD individuals [36].

Notably, the Wnt/mTOR pathway has been suggested as a common link between ADHD and sporadic Alzheimer's disease, indicating shared molecular pathways that may influence neuronal function and lifespan alterations [37]. This hypothesis underscores the complexity of neurodevelopmental disorders and the potential overlap in molecular pathways implicated in different conditions. Moreover, the involvement of mast cells in neuroinflammation and their potential role in ADHD pathogenesis adds another layer of complexity to our understanding of the disorder [38].

In summary, the intricate network of intracellular kinases and signaling pathways associated with ADHD underscores the multifactorial nature of the disorder. From mTOR and GIT1 to BDNF and CREB signaling, each component plays a unique role in shaping the neurobiological landscape of ADHD. Understanding these molecular mechanisms not only enhances our knowledge of the disorder but also paves the way for the development of targeted therapeutic strategies aimed at modulating these pathways to alleviate ADHD symptoms.

Transcription Factors Associated with ADHD

Research has shown that genetic predisposition plays a significant role in the development of ADHD [39]. Studies have identified genome-wide significant risk loci associated with ADHD, highlighting the importance of genetic factors in the etiology of the disorder [39]. Furthermore, investigations into DNA methylation patterns have revealed specific changes in genes like VIPR2 and MYT1L, which are involved in neurotransmission regulation, suggesting a link between epigenetic modifications and ADHD [40].

The overlap between ADHD and other neurodevelopmental disorders, such as autism spectrum disorders, indicates shared genetic and molecular pathways contributing to these conditions [41]. Genome-wide association studies have not only identified candidate genes associated with ADHD but have also shed light on fundamental processes like cell division, neuronal migration, and transcriptional regulation that are implicated in the disorder [42]. Additionally, variations in genes like the norepinephrine transporter have been linked to altered transcription, potentially increasing the risk for developing ADHD [43].

Moreover, the interaction between estrogen receptor genes and neurodevelopmental genes has been suggested to influence ADHD pathophysiology, although the precise mechanisms remain to be fully elucidated [44]. Studies have also highlighted the role of transcription factors like RFX family members in neurodevelopmental disorders, including ADHD, emphasizing their importance in central nervous system development [45]. Furthermore, the Forkhead box P2 (FOXP2) gene region has been associated with ADHD risk loci, indicating its potential involvement in the disorder [46].

Epigenetic profiling studies have identified DNA methylation patterns that differentiate ADHD trajectories, implicating genes involved in neural development and intellectual disability [47]. Additionally, polymorphisms in genes like STS have been linked to ADHD and shown to influence mRNA expression in the brain, suggesting a regulatory role in the disorder [48]. The association of genetic variants in dopamine transporter genes with ADHD further supports the involvement of transcription factors like Rps3a-2-homol-D in mediating ADHD-related mechanisms [49].

Furthermore, the identification of brain-specific enhancers within genes like ADGRL3 has provided insights into the genetic susceptibility of ADHD [50]. Sleep-related traits have also been linked to ADHD comorbidity, with shared genetic risk factors and molecular mechanisms contributing to both conditions [51]. Additionally, dysregulation of the Nr3C1-Bhlhb2 axis has been implicated in ADHD development, highlighting the involvement of gene regulatory networks in the disorder [52].

Understanding the role of transcriptional regulation in ADHD not only provides insights into its etiology but also offers potential targets for therapeutic interventions aimed at modulating gene expression and improving outcomes for individuals with ADHD.

In conclusion, research on growth factors, cell receptors, intracellular kinases, and transcription factors associated with ADHD has revealed a complex interplay between genetic, epigenetic, and molecular factors contributing to the pathogenesis of the disorder.

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