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Some physiological hormones in relation with autism disease in children boys: A review

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ABSTRACT

Autism is a neurodevelopmental disorder with unclear pathogenesis. Children with autism are classically characterized by deficits in language and social interactions as well as displays of odd or repetitive behaviors. Though historically considered relatively rare, the Centers for Disease Control and Prevention's (CDC) Morbidity and Mortality Weekly Report currently estimates that an average of 1 in 111 children in the U.S. have an autism spectrum disorder (ASD), with a gender bias of 4–5 times more males than females having ASD (Rice 2009). Despite this relatively high prevalence, our understanding of the neurodevelopmental biology and pathophysiology of these disorders remains limited. Many clinical observations and hormone studies have suggested the involvement of the neuroprotective hormone ghrelin in autism and other hormones such as: growth hormone (GH), leptin, cortisol, serotonin and oxytocin.

Keywords: Autism, Ghrelin, Oxytocin, Growth hormone, Serotonin, Leptin, Hydrocortisone.

Introduction

Autism spectrum disorders (ASDs) are a group of heterogeneous neurodevelopmental disorders that are classified as pervasive developmental disorders. ASDs are usually characterized by clinical manifestations of delayed or abnormal language development, deficits in social interaction, repetitive behaviors and restricted interest (Levy et al., 2009).

The pathogenesis of autism is not completely understood; however, a genetic origin has been recognized, and potential roles for both environmental factors and immune dysfunction have also been reported (Levy et al., 2009). Hormonal dysregulation in autism remains a strong candidate, as a wide range of hormonal abnormalities have been identified in autistic children. This finding indicates the significant involvement of the hypothalamic pituitary adrenal axis in the pathophysiology of the disease (Levy et al., 2009). Previous studies have shown that people with autism have abnormal levels of various hormones and neuroactive substrates such as ghrelin, leptin, serotonin, oxytocin, cortisol, and dehydroepiandrosterone (DHEA). Examining biomarkers may give us ways to identify individuals who demonstrate specific developmental.

Ghrelin

A significant volume of scientific evidence suggests a possible role for the hormone ghrelin in autism. Ghrelin is a 28-amino acid peptide that stimulates growth hormone (GH) release from the anterior pituitary gland (Asakawa, et al., 2001). Ghrelin has a wide range of physiological functions, and it represents a molecular link between peripheral metabolism and brain cognition. The hippocampus, which is the main (CNS) and plays an important role in memory and learning (Sato et al., 2009), is also affected in autism (DeLong, 1992). Moreover, ghrelin plays target of action for ghrelin in the central nervous system an important role in synaptogenesis, mainly in the hippocampal area (Diano et al.,2006) and abnormal synaptogenesis in this area has been reported in autism (Bourgeron, 2009). Ghrelin, on the other hand, is the best-known orexigenic hormone. In addition to its appetite-regulating effects, ghrelin increases growth hormone secretion, reduces somatostatin secretion, lowers mean arterial

pressure, and increases cardiac output by reducing systemic vascular resistance through vasodilation (Nakai et al., 2003).

Ghrelin has proliferative and anti-apoptotic effects in the CNS, especially during oxygen/glucose deprivation; thus, it may protect the hypothalamus against reactive oxygen species, which have recently been linked to autism (Adams et al., 2011).

In addition, ghrelin protects primary cortical neurons from apoptosis induced by glutamate, an amino acid that is elevated in autistic children (Shimmura et al., 2011). Alteration of plasma glutamate and glutamine levels in Ghrelin influences the sleep-wake cycle, and its levels increase in the first hours of sleep-in healthy individuals (Dzaja et al.,2004). Additionally, ghrelin is the most powerful orexigenic peptide and is known Sleep and appetite disturbances, and hyperactivity are among the frequent problems facing children with autism (Geier and Geier, 2007). These observations, taken together, prompted us to hypothesize that ghrelin could be involved in the pathogenesis of autism. It wasn't clearly distinctive in the literature which of those actions mediated through AG and which were mediated through DG despite AG is considered generally the active form.

Study by (Al-Zaid et al., 2014), demonstrate low AG (acyl ghrelin) and DG (des-acyl ghrelin) levels in autistic children. Considering the capacity of ghrelin to affect neuroinflammatory and apoptotic processes that are linked to autism, this study suggests a potential role for the hormone ghrelin in the pathogenesis of autism.

Leptin

Leptin is in the same protein family as interleukin (Il)-6, an inflammatory cytokine, and its dysregulation has been associated with psychopathology, and evidence suggests that this relationship is related to leptin's inflammatory function (Baumann et al., 1996). It has been implicated in various psychiatric disorders such as schizophrenia (Takayanagi et al., 2013), major depressive disorder (Burrows et al., 2023), and bipolar disorder (Fernandes et al., 2016) Te role of leptin in ASD has also become a subject of interest, but the underlying mechanisms remain to be determined. Other adipokines, which are inflammatory mediators mainly secreted by adipose tissue and some immune cells, have also garnered increasing attention in ASD research. Adipokines have the potential to impact immune responses and are believed to play a role in the pathophysiology of ASD (Pan and Kastin, 2007). Several studies have reported alterations in adipokine levels in ASD, including downregulation of adiponectin (Fujita -Shimizu et al., 2010), among others. However, the findings regarding adipokines in ASD are inconsistent, possibly due to differences in patient populations, variations in methodologies, or small sample sizes lacking statistical power.

Study by (Lei Chen et al., 2024) examined the significant increase in serum leptin levels in ASD patients compared to healthy controls. Additionally, a meta-analysis of 19 studies with a total sample size of 740 patients and 1456 controls revealed alterations in leptin and progranulin levels in individuals with ASD. The analysis highlights that the significant difference in leptin levels primarily focuses on plasma and suggests a potential influence of publication year and latitude on the observed heterogeneity. It is important to note that the results for progranulin present limitations, requiring further studies for confirmation. It is widely recognized that children with ASD have a higher risk of overweight or obesity compared to those with typical development (Zheng et al., 2017). Tis study explored the role of leptin, an adipocyte-derived factor, in ASD and its potential involvement in the development of the disorder. While previous research supports the critical role of leptin as a regulator of food intake and energy expenditure, recent studies have proposed that dysregulation of leptin is a mechanism for psychopathologies, including ASD (Blardi et al., 2010). Tis proposal is based on the observed comorbidity between obesity and various mental illnesses (Simon et al.,2006). Similarly, the hormone leptin represents another potential link between ghrelin and autism, as these hormones have an inverse relationship (Ashwood, et al, 2008).

Leptin inhibits ghrelin transcription in a dose dependent manner, thus reducing ghrelin levels (Zhao et al., 2008), and leptin levels have been reported to be significantly higher in children with autism. These elevated leptin levels may be associated with decreased ghrelin levels in autism.

Serotonin

Serotonin (5-hydroxytryptamine, 5-HT), Biosynthesized from the amino acid tryptophan, is mainly found in serotonergic neurons, enterochromaffin cells, and blood platelets. 5-HT is a crucial hormone and neurotransmitter that controls a number of neurobiological processes in the central nervous system (CNS). These processes are mediated by a group of serotonin receptors (5-HTRs), which are classified into seven subfamilies (5-HT1–7R). The 5-HTRs belong to a family of G protein-coupled receptors (GPCRs), except for 5-HT3R, which is a ligand-gated ion channel. 5-HT system plays a

fundamental role in neurite outgrowth, dendritic spine morphology, shaping neuronal circuits, synaptic transmission, and synaptic plasticity. Given the roles of 5-HT, a variety of diseases such as depression, anxiety, schizophrenia, and neurodevelopmental disorders (e.g., ASD, fragile X syndrome, and Rett syndrome) have a close relation with regulation of 5-HT systems (Green, 1948; Whitaker-Azmitia, 2001; Pithadia et al., 2009). As therapeutic targets in numerous brain diseases, 5-HT has thus become a highly important class of biogenic amines. In this review, we will focus on recent Repeated findings of increased serotonin levels in approximately one-third of children with ASD has led some to believe that dysfunctional serotonin signaling may be a causal mechanism for the disorder (Harrington et al.,2013). Abnormalities in the brain serotonin system are reported in ASD, including evidence of altered serotonin synthesis and receptor binding, as well as dystrophic serotonergic axons (Azmitia et al., 2011).

Oxytocin

oxytocin is a nanopeptide (i.e. it has nine amino acids). Oxytocin is synthesized in magnocellular neurons in the paraventricular nucleus and the supraoptic nucleus of the hypothalamus. It is released into the bloodstream by way of axon terminals in the posterior pituitary. Oxytocin is released both peripherally, where it is involved in milk let down and the facilitation of uterine contractions, and centrally, where it acts as a neuromodulator (Green and Hollander, 2010).

Blood oxytocin levels are also a focus of ASD research. Children with ASD have lower average levels of blood oxytocin in comparison to typically developing children matched for age. In contrast, a study of adults with ASD suggests that oxytocin levels are higher at baseline in

adults (Jansen et al., 2006). The serotonin and oxytocin systems interact in the brain, both during development and in adulthood. The serotonin system regulates oxytocin release in human adults, as evidenced by the increased oxytocin levels after treatment with 3,4-methylenedioxymeth-amphetamine (popularly known as 'Ecstasy'), a drug that causes the release of serotonin (Eaton et al., 2012).

Growth hormone

Increased head growth has frequently been reported in children with autism/ASD, and particularly dramatic brain overgrowth in early life. Increased statural or ponderal growth in childhood has also been reported in children with autism/ASD; however, the data are inconsistent (Lainhart, 2003). Although it has been hypothesized that androgenic hormones may play a role in autism because of the preponderance of male cases (Manning et al., 2001).

Increasing evidence indicates that growth factors modulate motor, emotional, and cognitive functions, which may explain various clinical manifestations of psychiatric disorders. Furthermore, alterations in the expression levels of growth factors during embryogenesis are linked to the pathophysiology and clinical manifestations of various neuro-developmental disorders, including ASD (Amaral et al., 2008).

However, ghrelin and GH are strongly connected, as ghrelin is known for its capacity to stimulate the release of GH (Kojima et al., 2005). Additionally, in an animal model of induced GH deficiency, gastric ghrelin mRNA levels and circulating ghrelin levels were significantly reduced, suggesting that ghrelin gene expression is influenced by GH status (Caminos et al., 2002)

Cortisol hormone

Hydrocortisone, also known as cortisol, is a short-acting Glucocorticoid Cortisol is the main HPA axis hormone secreted by the adrenal cortex, and influences metabolism, cognition, and behavior. Recently, a plethora of studies have tried to confirm the correlation between peripheral cortisol and autism spectrum disorder (ASD). After oral administration, hydrocortisone is readily absorbed with a biological half-life of approximately l.0–1.5 h before metabolism by the liver, used in the acute phase of Persistent Fetal Circulation to achieve hemodynamic stability in patients who develop systemic hypotension. In addition to its anti-inflammatory and blood pressure stabilizing effects, hydrocortisone has been shown to decrease oxidative stress, increase the levels of Extracellular Superoxide Dismutase of PPHN lambs exposed to 95% oxygen for 24 hours (Young et al., 1999). In neonatal lambs with PPHN ventilated with 100% oxygen, hydrocortisone treatment improved oxygenation, normalized PDE5 activity, and decreased oxidative stress. Obvious heterogeneity across studies was found in the overall analysis. Peripheral cortisol levels were significantly elevated in ASD patients compared with controls in the absence of obvious heterogeneity (Bozkurt et al., 2021; Gao et al., 2022). Study by (Ćurin et al., 2003) showed Individuals with autism had significantly lower serum concentrations of cortisol ($p < 10-6$), and significantly higher concentrations of ACTH ($p = 0.002$).

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