Acyl Ghrelin Levels in Autistic Males

Thesis

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List of Abbreviations

Abb.	Full term
AG	Acylghrelin
ASD	Autism spectrum disorder
DSM5	Diagnostic and statistical manual of pediatrics
GH	Growth hormone
GHBP	Growth hormone binding protein
IGF	Insulin growth factor
IQ	Intelligence quotient

INTRODUCTION

ASD is a neurodevelopmental disorder with unclear pathogenesis. Although genetic origin has been recognized, there is a known potential role for environmental factors, immune dysfunction and hormonal dysregulation. Surprisingly little attention has been given to the role of hormones in the pathogenesis of ASD which is usually characterized clinically by impaired social interaction, repetitive behaviour, restricted interest ***(DSM-5, 2013).***

Acylghrelin is a peptide hormone secreted predominantly from the stomach and considered the most powerful orexigenic peptide ***(Tang and Goldman, 2002).*** In addition ghrelin can stimulate (GH) release from the anterior pituitary by activating GH secretagogue receptor ***(Askawa et al., 2001).*** Also ghrelin exerts neuroprotective effects, inhibits apoptosis in hypothalamic neurons and has positive effects in learning and memory ***(Adams et al., 2001)***. There is significant reduction in both ghrelin and GH in autism as GH levels can affect ghrelin gene expression and thus can influence plasma ghrelin levels ***(Caminos et al., 2002).***

Alteration in plasma ghrelin level may also be a part of hormonal dysregulation of the androgens, leptin and GH ***(Martos-Moreno et al., 2010).*** Previous studies have shown that androgen levels are significantly higher in autistic children ***(Geiere and Geier, 2007).*** At the same time, it is an established

fact that the plasma ghrelin levels are negatively correlated with high plasma testosterone level ***(Tschop et al., 2001).*** Another hormone that has been studied is leptin, where it has been found that elevated plasma leptin levels is associated with reduced plasma ghrelin levels ***(Ashwood et al., 2008).*** Alteration in both ghrelin and leptin is associated with adiposity ***(Bellone et al., 2012).*** Despite the fact that children with autism have increased weight despite low ghrelin (orexeginic hormone) ***(Falorni et al., 1997)*** and high leptin levels (anorexigenic hormone) this can be explained by impairment in central processing of such periopheral signals or involvement of many hormones other than ghrelin and leptin ***(Hage et al., 2011).***

Aim of the Work

This study aims at investigating the acyl ghrelin and GH levels in autistics comparing males to females and in atrial to further elucidate the associated hormonal dysregulation in such cases.

Chapter 1

AUTISM

Autism spectrum disorders (ASD) is a neurodevelopmental disorder that charactrised by persistant impairment of social interaction, deficits in verbal and non-verbal communication, and restricted repetitive and stereo-typed patterns of behavior and interests. Manifestation of ASD must be encountered early in life(<30-36months) although they might be not fully developed until later in life when the social demands far exceeds child abilities. Meanwhile, they should lead to clinically impairment in social, occupational or other crucial domains of functioning. The diagnosis might be difficult as the child gets older because he or she learn how to hide some critical diagnostic manifestation. ASD has many specifiers that make each child suffering from it has a unique and necessitate individualization of diagnosis and management plan ***(DSM-5, 2013)***.

Etiology:

The exact cause of ASD is still unknown but what is known nowadays that it results from interaction of multiple factors such as genetic, environmental, hormonal and autoimmune factors ***(Zaky, 2015).***

1. Genetic factors:

Genetic factors are crucial for development of ASD as heritability from family and twin studies provide evidence for a strong genetic contribution. Monozygotic twins are much more concordant for ASD than dizygotic twins. There is one ASD linked locus in almost every chromosome more linked to it than others such as those on X,2,3,7,11,15,17 and 22. It seems that such linked genes are essential for normal development of neurocircuits concerned with communication, emotional expression, social interaction which are impaired in autism ***(Dawson, 2007).*** On the other hand some autistic children suffer from comorbid genetic conditions as Down syndrome, fragile x syndrome, phenylketonuria, tuberous sclerosis and others. Also, it is worthy to mention that at the time of zygote formation, the older the parental age, the higher the risk of occurrence of ASD especially on the paternal side because sperm production occurs throughout life that makes them more vulnerable to be negatively influenced by mutations ***(Croen et al., 2007)***.

2. Environmental factors:

There are many factors associated with increased risk of autism such as antenatal, natal, postnatal factors.

A. Antenatal factors:

Antenatal risky factors for the subsequent development of ASD include maternal age above 35 years ***(Hadjkacem et al., 2016)***, gestational hypertension ***(Haltmann et al., 2002)***, gestational diabetes ***(Dodds et al., 2011),*** threatened abortion ***(Glasson et al., 2004)***, antepartum hemorrhage, preeclamia.

B. Natal factors:

Natal risky factors for subsequent development of ASD include cesarean section ***(Burstyn et al., 2010)***, prematurity, intrapartum hypoxia.

C. Postnatal factors:

Postnatal factors include low birth weight ***(Haglund & Kallen, 2011)***, post partum hemorrhage, respiratory distress syndrome, indirect hyperbilirubinemic encephalopathy, intracranial hemorrhage ***(Szpir, 2006).***

3. Autoimmune factors:

Ghrelin is known to play an important role in immune modulation in the CNS; in experimental autoimmune encephalomyelitis (EAE), ghrelin inhibits the production of the proinflammatory cytokines tumour necrosis factor-alpha (TNF-a), interleukin-1 (IL-1) and IL-6, with microglia being the main target cells. Microglia are the main immunocompetent cells in the immature CNS and, in turn, can acquire various phenotypes that determine the CNS consequences of inflammation. It has been

suggested that autism is a result of CNS derangements due to chronic inflammatory reactions ***(Hagberg et al., 2012)***.

Ghrelin has been found to serve as an anti-inflammatory agent for the control of human CNS disturbances triggered by the production of pro-inflammatory cytokines. Thus, the findings of the present study, which revealed significantly lower plasma ghrelin levels in autistic children, strongly suggest a potential role for ghrelin in the pathophysiology of autism. However, the neuronal influence of leptin cannot be excluded, as leptin influences neurons by altering their structure and plasticity ***(Matochik, 2005)***.

There is a mounting evidence of an immunological dysfunction in children with autism. Studies have demonstrated an increased frequency of autoantibodies against brain/central nervous system proteins ***(Singh et al., 2004),*** increased proinflammatory cytokine levels, and decreased anti-inflammatory cytokine levels ***(Ashwood et al., 2004)*** and skewed TH2 cytokine profiles. An altered immune response may impact other biological systems including the neuroendocrine and nervous systems and vice versa. One of the most interesting of the neuroendocrine mediators shown to have an effect on the immune system is leptin ***(Jyonouchi et al., 2002)***.

Leptin shares structural and functional similarities with several cytokines, many of which are involved in neurodevelopment, including IL-6 and IL-12 ***(Zhang et al., 1994).***While adipocytes are the major source of leptin

production, lymphocytes have also been demonstrated to produce leptin ***(Sanna et al., 2003).*** Several studies suggest a role for leptin in immune modulation. Similarly, humans with congenital leptin deficiency are more susceptible to fatal infections during childhood due to defective cell mediated and humoral immunity ***(Ozata et al., 1999).*** In animals with autoimmune diseases, leptin deficiency has been shown to shift the immune response from TH1 to TH2, leading to a protective effect against inflammation ***(Busso et al., 2002).*** Importantly, inflammatory cells themselves secrete leptin, which may further foster the inflammatory process ***(Fantuzzi et al., 2005).***

4. Hormonal factors:

There are changes in the level of multiple hormones in ASD. Such hormones include androgens, leptin, growth hormone, acyl ghrelin. These changes might be involved in the etiology of ASD and will be discussed later in details.

Diagnosis:

ASD is diagnosed according to the latest diagnostic criteria in diagnostic and statistical manual of mental disorders (DSM-5, 2013) which are as follows:

A. Persistent deficits in social communication and social interaction.

B. Restricted, repetitive pattern of behavior, interest, or activities.