

SHORT COMMUNICATION

Neuroendocrine contribution to autism etiology

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Abstract

OBJECTIVES: Autism spectrum disorder (ASD) is a set of heterogeneous neurodevelopmental conditions characterized by early-onset difficulties in social communication and unusually restricted, repetitive behavior and interests. One of the main features of autism is the unequal sex distribution, with higher prevalence in boys. There is evidence that in critical prenatal period testosterone and its metabolites play crucial role in masculinization of brain structures with the consequences on cognitive and behavioral style. In general human population males are more systemized while females are more empathized. According to the hypermale brain theory the behaviors seen in autism are exaggerations of typical sex differences and therefore exposure to high levels of prenatal testosterone might be a risk factor for autism. Oxytocin as a neuropeptide affecting social behavior is considered a prosocial hormone and might be protective in autism development. The aim of this study was to reveal differences in plasma levels of oxytocin between autistic and healthy populations in Slovakia.

METHODS: ASD children were diagnosed by ADOS and ADI-R diagnostic tools, only boys were included in this study.

RESULTS: Oxytocin levels were lower in the prepubertal and also in the pubertal boys with ASD, while testosterone levels were higher only in the prepubertal boys with ASD when compared with boys from general population.

CONCLUSION: Our work brought contribution to the investigation on the influence of neuroendocrine milieu to ASD phenotype.

INTRODUCTION

Autism spectrum disorder (ASD) is a set of heterogeneous neurodevelopmental conditions characterized by early-onset difficulties in social communication and unusually restricted, repetitive behavior and interests. The wide variety of disorders related to autism is collectively named the autism spectrum disorders (ASD). Autism is characterized by early-onset developmental delay before the age of three, followed by

the specific psychopathology: impairments in social interaction, communication, and repetitive, restrictive behavior (Lai *et al* 2014). During the last decade the prevalence of autism has been significantly increased (Lai *et al* 2014). The worldwide population prevalence is about 1% (Lai *et al* 2014). Increased awareness, recognition and better diagnostics are not the only reasons explaining increased ASD incidence. The real raise of the disease is probably caused by increasing parental age associated with *de novo* mutations in germ

line cells. Autism is very likely linked with changes in expression of developmental genes due to exposure to environmental toxins. Increasing ASD prevalence is followed by bigger interest of scientific community what is mirrored by growing numbers of reports published in medical databases. In spite of the diligent effort of many research teams, the exact pathological mechanism of ASD still remains uncovered. Many factors which regulate brain development with consequences on the phenotype are known to be altered in autism. Autism is evolutionary relatively young disease responsible for abnormal development of central nervous system. Development of central nervous system occurs in predefined stages. Disruption of developmental trajectory can be caused by a combination of genetic and epigenetic factors, with impact on neurogenesis, neuronal apoptosis as well as synaptogenesis and synaptolysis resulting into the impairment of neuronal connectivity and function (Rubenstein 2011). In the clinical field of many psychiatric disorders, a fundamental puzzle has been characteristic sex differences in their prevalence. Males are more vulnerable to the development of attention-deficit/hyperactivity disorder, conduct disorder, autism spectrum disorders, as well as learning disabilities. Females are more vulnerable to the development of major depressive disorder, as well as several anxiety disorders (APA 2013). This phenomenon has led to frequent invocation of sex hormones in relation to neurodevelopmental disorders.

One of the main features of autism is the unequal sex distribution, with higher prevalence in boys. Male predominance is four times higher than female, however with the growing severity of cognitive deficits the gender inequality is decreasing the less severe cognitive impairments result in increased gender inequality. Individual behavioral traits or specific cognitive abilities are the result of a combination of genetic, hormonal and environmental factors (Durdiakova *et al* 2011). There is evidence that in critical prenatal period testosterone and its metabolites play crucial role in masculinization of brain structures with the consequences on cognitive and behavioral style (Durdiakova *et al* 2011; Lutchmaya *et al* 2002; Knickmayer *et al* 2005) In general human population males are more systemized while females are more empathized. According to the “hypermale brain theory” (Baron-Cohen *et al* 2011; Wen & Wen 2014) the behaviors seen in autism are exaggerations of typical sex differences and therefore exposure to high levels of prenatal testosterone might be a risk factor for autism.

It is an empirical experience that ASD girls with more severe impairment are brought to diagnostic attention and also that the siblings of female patients had higher autism symptom scores than siblings of male patients. That implies the sex specific mechanisms. One suggestion is female protective effect – genetic or hormonal, or male risk factor – genetic or hormonal. A convincing factor for gender differences in the ASD is the consistently differential exposure to immature brain to hormones.

Testosterone is considered the main male sexual hormone. Increased androgen activity has often been considered a potential etiological factor in pathogenesis of aggressive behavior. Oxytocin is involved in social behavior and particularly in the formation of mother-infant and adult-adult pair bonds, thus it is considered the prosocial hormone and might be protective in autism development. The aim of this study was to compare testosterone and oxytocin levels in children with autism and age matched children of general population in Slovakia.

PARTICIPANTS AND METHODS

The study was approved by the Ethic Committee of the University Hospital and Faculty of Medicine, Comenius University in Bratislava. Written informed consent was obtained from the parents of all children involved in this study. Children were diagnosed by ADOS-2 and ADI-R diagnostic tools.

Venous blood were taken from boys with autism in the local Neurological Centre for Children and Adults in Bratislava. Blood of control children was taken by their pediatrician. The blood samples of all children were obtained during the same daily interval from 8.00–9.00 a.m. Testosterone and oxytocin levels in children were analyzed in plasma using ELISA method (DRG Diagnostics, Germany). Oxytocin (Figure 1) and testosterone (Figure 2) were measured in 105 boys with ASD (83 under the age of 10 and 22 above the age of 11) and in 111 control boys (56 under the age of 10, 55 above the age of 11). Boys were divided into two groups – prepubertal and pubertal. During the silent period between ages 2–10 the levels of testosterone are relatively stable and very low in boys. At the beginning of puberty, male testosterone levels increase with great interindividual variability.

Data were statistically analyzed with Man Whitney test and presented as mean + SEM.

RESULTS

Oxytocin levels (Figure 1) were lower in boys with ASD compared to control boys either in the whole sample as well in prepubertal and pubertal age groups. Testosterone levels (Figure 2) were lower in ASD boys in case all boy participants were considered. As the boys enter puberty there are great interindividual differences in testosterone release pattern, therefore we have examined testosterone levels in two age group separately. In prepubertal age boys higher testosterone levels were found, while in boys who entered puberty no difference was observed.

DISCUSSION

Literature defines endophenotypes as biologic indicators typical for given disease. Oxytocin and testosterone are considered as typical endocrine endophenotypes in

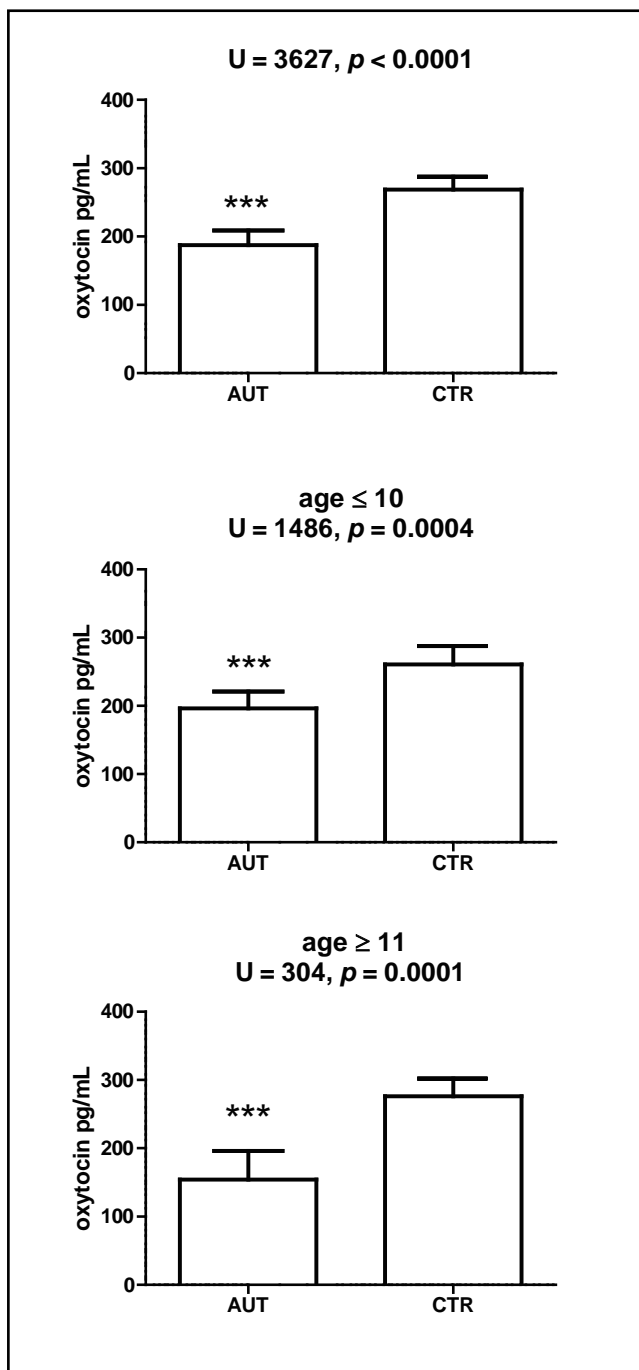


Fig. 1. Plasma oxytocin levels (pg/mL) in ASD boys (AUT) and control boys (CTR) together and in groups divided by age. Data presented as mean + SEM.

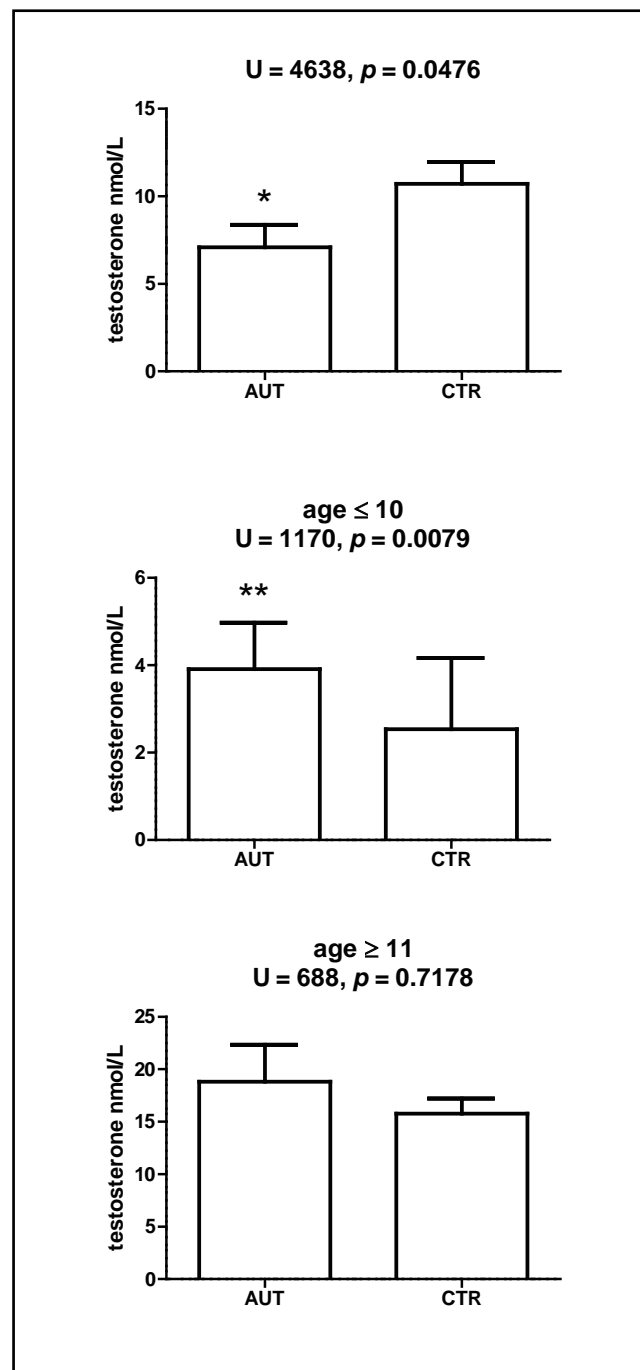


Fig. 2. Plasma testosterone levels (pg/mL) in ASD boys (AUT) and control boys (CTR) together and in groups divided by age. Data presented as mean + SEM.

individuals with autism (Mohdal *et al* 1998). The aim of this study was to compare testosterone and oxytocin levels in blood in boys with ASD and healthy boys in general population. The statistical analysis was done for all boys in both compared groups and then it was performed for the boys in prepubertal and pubertal ages separately. During prepubertal sexually silent period boys show relatively stable low testosterone levels while with the onset of adolescence testosterone levels rapidly increase and show great interindividual differences.

Our results showed lower oxytocin levels in ASD boys in both age groups. We found higher testosterone levels in ASD boys only in the group of prepubertal boys which was expected due to the aforementioned reasons.

Autism is diagnosed four times more frequently in males than in females. Considering gender differences in cognitive profile in normal population, typical male cognitive profile is described as less emotional and more systemic, while females are more emotional and less systemic. Cognitive profile of ASD male patients was

found to be even more systemic in comparison to males from normal healthy population and less empathic compared to males from normal healthy population. These observations lead into the assumption that testosterone as a male sex hormone which contributes to organization of brain structures can play role in etiology of ASD and can be responsible for extreme male brain characteristics in autism (Baron-Cohen 2008). Previous studies found inverse correlations between fetal testosterone and the ability to read nonverbal communication (Knickmeyer *et al* 2005). Also positive correlations between fetal testosterone and autistic traits were observed (Knickmeyer *et al* 2006; Auyeung *et al* 2009). In addition increased levels of prenatal testosterone may cause excellent performance at systemizing skills (analyzing of object and structures, excellent memory, collecting facts) and lack of empathy and communication deficits in patients with Asperger syndrome compared to control healthy individuals (Baron-Cohen *et al* 2002).

Oxytocin is well known as a prosocial hormone increasing trust and interaction among unknown individuals. Our recent results showed that male ASD individuals have decreased oxytocin levels in blood plasma (Husarova *et al* 2013). Randomized controlled trials of oxytocin interventions in autism yielded potentially promising findings (Preti *et al* 2014). Hollander *et al* (2007) found improved affective speech recognition following oxytocin infusion in comparison with placebo infusion. Anagnostou with colleagues (2012) found significant improvements on the Reading the Mind in Eye Test after 6 weeks of oxytocin administration versus placebo in adults with ASD. There were some other studies providing the evidence of decrease in diagnostic severity after oxytocin intervention (Andari *et al* 2010; Guastella *et al* 2010; Dadds *et al* 2014).

The main limitation of this study is the fact that the plasma levels of the studied hormones do not exactly reflect the concentrations in brain. There is no possibility to measure testosterone and oxytocin concentrations in cerebrospinal fluid in children due to ethical reasons, therefore we can only rely on those from peripheral blood concentrations.

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