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Testosterone and explosive aggression in autism spectrum disorders

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Abstract

Autism spectrum disorders (ASD) are a set of heterogeneous neurodevelopmental conditions, characterized by early-onset difficulties in social communication and unusually restricted, repetitive behavior and interests. Children with ASD have a high rate of irritability and aggressive symptoms which have significant impact on their lives, families and society. The etiology of aggression in humans is likely complex and includes both biological and behavioral causes. Biological approaches have focused on hormones and neurotransmitters that are hypothesized to contribute to the etiology and clinical manifestation of aggressive behavior in humans. Testosterone is a male sex hormone and some studies suggest that it can play a role in the complex etiology of aggressive behavior. Two specific subtypes of aggression have been identified: explosive and non-explosive. Explosive aggression is accompanied by a raged affect and is usually more dangerous and not immediately responsive to behavioral treatment. In our review we would like to provide current findings and discuss potential limitation of research in this area. We propose to determine bio-behavioral model of explosive aggression in children with ASD which will predict which children will be most responsive to potential antiandrogen therapy and behavioral therapy.

INTRODUCTION

Autism spectrum disorders (ASD) are a set of heterogeneous neurodevelopmental conditions, characterized by early-onset difficulties in social communication and unusually restricted, repetitive behavior and interests. Autism is the most genetically influenced neuropsychiatric disorder with heritability of approximately 90%. The worldwide population prevalence is about 1% (Lai *et al.* 2014; Kelemenova & Ostatnikova 2009). A recent large-scale study found that prevalence of aggression in children with ASD was 68% of parents reporting and 49% of non-caregivers (Kanne & Mazurek 2011). These behavior disorders often place children at risk of harming themselves and others and are the single most cited reason for costly inpatient hospitalization, long-term resi-

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dential placement, and restrictive living and treatment environments. Moreover all these factors lead to psychological disturbance in families along with social and economical costs to society (Hartley *et al.* 2010).

Clinical research, influenced by the work of Feshbach and others has frequently referred to two forms of aggression in humans (Dodge *et al.* 1997; Feshbach 1971; Scarpa *et al.* 2010). The first form is called *affective, reactive, defensive, impulsive, or hot-blooded aggression*. This type of aggression is defined as a violent response to physical or verbal aggression initiated by others that is relatively uncontrolled and emotionally charged. In contrast, the second form of aggression is referred to as *predatory, instrumental, proactive, or cold-blooded aggression*. This type of aggression is characterized as controlled, purposeful aggression lacking in emotion that is used to achieve a desired goal, including escape of aversive events, access to positive reinforcing events, and the domination and control of others. Although other terms have been used to differentiate these two forms of aggression, (e.g. Atkins & Stoff, Zukov *et al.* 2008) for purposes of this paper, we will use the terms *explosive aggression* to refer to aggression accompanied by high arousal and rageful affect and *non-explosive aggression* to refer to aggression in the absence of high arousal and rageful affect.

BACKGROUND

Etiology of aggression

Aggression in humans is a function of a complex interplay between biological (neurochemical imbalance in the brain) and behavioral (operant reinforcement contingency that maintains the behavior) causes. Diagnosis and treatment of aggression and other problem behavior in ASD should include bio-behavioral approaches and involve inter-professional cooperation between physicians/psychiatrists and psychologists. This model takes into consideration the multi-faceted nature of the origins of aggression rather than relying on one model (Frazier *et al.* 2010; Mace & Mauk 1995).

Biological approaches have focused on hormones and neurotransmitters that are hypothesized to contribute to the etiology and clinical manifestation of aggressive behavior in humans. This research has led to specific pharmacotherapeutic approaches to address neurochemical imbalances in the brain. For example, dopamine blockers such as antipsychotics (e.g. risperidone) have been observed to be effective in treating some aspects of autism, specifically hyperactivity, stereotypies, aggression, and self-injury (Young *et al.* 1982). Some studies have shown that levels of dopamine metabolites in cerebrospinal fluid (Gillberg *et al.* 1983) are significantly elevated in individuals with autism. Risperidone blocks dopamine receptors in some areas of brain (Kozielska *et al.* 2012) and may result in decreased dopamine effect which may lead to decreased aggression in individuals with autism. The literature also suggests testosterone may be involved in the etiology of aggression in humans as another contributing biological factor.

Physiology of testosterone

Testosterone is a male sex hormone, in men the main production of testosterone is localized to Leydig cells in the testes. Half of testosterone in females is generated by the ovaries, while the rest by the cortex of suprarenal glands. Biosynthesis of testosterone occurs also in other tissues, even in some regions of the brain (Durdiakova *et al.* 2011).

Testosterone is a steroid hormone metabolized from cholesterol. In blood circulation, testosterone binds to the sex hormone binding globulin (SHBG) and is, thus, protected from metabolic degradation but is also biologically inactive. Only a small fraction of the hormone is free and active (able to bind to its receptor or to be further metabolized). In some target tissues (i.e., adipose tissue, brain), aromatase catalyzes the conversion of testosterone to the female sex steroid hormone estradiol. The effect is then mediated via estrogen receptors. Alternatively, 5α-reductase reduces testosterone to more a potent androgen dihydrotestosterone (DHT) which also binds to androgen receptors. Testosterone and dihydrotestosterone are ligands of the nuclear androgen receptor (Durdiakova *et al.* 2011).

Androgen and anabolic effects of testosterone are responsible for variety of morphological characteristics that are well described and widely known (Durdiakova *et al.* 2011). Testosterone is also known having effect on various behavioral and cognitive functions in humans. Individual behavioral traits or specific cognitive abilities are the result of a combination of genetic, hormonal and environmental factors (Durdiakova *et al.* 2011).

TESTOSTERONE AND AGGRESSION-CURRENT KNOWLEDGE AND POTENTIAL LIMITATIONS OF RESEARCH

In the following sections we would like to provide an overview of current knowledge about relationship between aggression and testosterone with special focus on children with ASD and moreover we would like to discuss potential limitations of current research studies. Firstly we will discuss the general hyperandrogeny-aggression link (A) and point out possible methodological problems leading to confusing findings in research about relationship between testosterone and aggression (B). We then review the potential for objective subtyping of aggression based on physiological measurements and relation of androgen activity to explosive aggression (C), and finally anti-androgen medications and their history of use in anti-aggressive indications (D).

A. Hyperadrogeny-aggression link

There is evidence that hyperandrogeny is related to aggression, however we have found only 2 studies (Tordjman *et al.* 1997; Pivovarciova *et al.* 2014) focusing

on the aggression-hyperandrogeny relation in children with ASD.

1. Testosterone and aggression in non-ASD population

Several studies have examined the relationship between salivary/plasmatic testosterone levels and aggression in individuals without ASD and found mixed results. Some of them describe no clear relationship between the plasma/salivary testosterone levels and aggressive behavior in populations of pre-pubertal children (Constantino *et al.* 1993), in male undergraduates (Campbell *et al.* 1997) and in healthy male adults (Anderson *et al.* 1992; King *et al.* 2005). However, there are studies showing strong positive correlations between testosterone (and testosterone precursor) levels in plasma/saliva and aggression (e.g., in populations of male children with conduct disorders, male/female adolescents and adults, and male prisoners (Barzman *et al.* 2013; Dabbs *et al.* 1987; Dmitrieva *et al.* 2001; Golubchik *et al.* 2009; Scerbo & Kolko 1994; van Goozen *et al.* 1998; Yu & Shi 2009).

2. Testosterone and aggression in ASD population

There are several studies investigating the relationship between testosterone and symptoms of ASD describing autistic brain as an extreme form of male brain (Krajmer *et al.* 2010; Baron-Cohen 2002; Lakatosova *et al.* 2010). However, as we mentioned above, we found only two studies showing an association between testosterone and aggression in these individuals.

Tordjman *et al.* measured plasma testosterone in nine patients with ASD compared to a group of neurotypical children. The nine children with ASD were divided into three groups comprised of those aggressive against others, those who are self-mutilating, and a third group that had the withdrawal characteristic of ASD. The group that exhibited aggression against others (termed explosive aggression by the authors) had plasma testosterone concentration values higher than any of the comparison subjects, however the other autistic patients showed normal adrenal androgen levels (Tordjman *et al.* 1997).

In our recent pilot study (Pivovarciova *et al.* 2014) only one of the three children with ASD engaged in aggression that co-occurred with rageful affect and indicators of high arousal during episodes of problem behavior. His plasmatic testosterone level was 2.07 standard deviations above the mean of the age and gender matched control group, indicating an abnormally high level of plasmatic testosterone.

B. Testosterone and aggression-possible explanations of various findings

The findings on a relationship between testosterone and aggression are mixed. These discrepant results may be due to several factors: (1) involvement of other components of androgen activity – f actors, other than total plasmatic testosterone levels- in modulating androgen activity (e.g., function of enzymes responsible for metabolism of testosterone, sensitivity of androgen receptors, levels of active/free testosterone in plasma); (2) involvement of other hormones in etiopathogenesis of aggression in humans (cortisol, vasopressin, oxytocin, serotonin and others); (3) existence of subtypes/classes of aggression; and (4) limitations in exact evaluation of aggressive symptoms.

1. Involvement of other components of androgen activity

Individual behavioral traits or specific cognitive abilities are the result of a conjunction of genetic, hormonal and environmental factors. Testosterone activity might be influenced in each step of its metabolic processing. Involvement of other factors, other than total plasmatic testosterone levels, in modulating of androgen activity can be one of the possible reason for mixed findings about relationship between testosterone and aggression. Except of the total plasmatic testosterone levels, androgen activity and effect can be modulated (1) by function of enzymes responsible for metabolism of testosterone (aromatase and 5-alpha reductase), (2) by sensitivity of androgen receptors and (3) levels of active/free testosterone in plasma. These factors have been discussed in recent reviews (Durdiakova *et al.* 2011) and several researchers point out that testosterone and its relationship to aggression should be studied in various stages of androgen activity. In a recent study individuals with more sensitive AR are more common among rapists and murders than a control group (Rajender *et al.* 2008). Higher activity of aromatase leads to lower levels of testosterone and higher levels of estrogens. Physical violence and verbal aggression have been positively correlated with peripheral testosterone and negatively correlated with peripheral estradiol levels in elderly women and men diagnosed with dementia (Orengo *et al.* 2002). Testosterone bound to SHBG is in inactive form and needs to be released to have an effect on tissues. Decreased blood SHBG levels means that more testosterone is unbound and the amount of free/active testosterone is greater which leads to higher androgen activity. Healthy women, those who expressed more aggression had lower levels of SHBG (Witte *et al.* 2009).

2. Complex interaction with other hormones

It is quite possible that testosterone is not the only one hormone that plays role in etiology of aggression/subtypes of aggression. Several neuroendocrinological studies revealed that there may be other hormones/neurotransmitters involved.

Triple imbalance theory of aggression describes hormonal findings in impulsive aggression in adults (cf. explosive aggression). It has been proposed that low levels of the neurotransmitter serotonin (5-HT), in combination with high testosterone/cortisol ratio may facilitate the impulsive subtype of aggression in particular (van Honk *et al.* 2010) as low 5-HT relates to impulsive behavior. Thus, a neurobiological profile of

low cortisol, and high testosterone levels, together with low 5-HT would predispose to impulsive aggression.

Some researchers also investigated *reactive/proactive aggression in children* (cf. explosive/non-explosive). Reactive aggression was strongly correlated with elevated cortisol in adolescents with conduct disorder (van Bokhoven *et al.* 2005). Lopez-Duran and colleagues (Lopez-Duran *et al.* 2009) evaluated cortisol reactivity in children and noted that subjects with patterns of reactive aggression had higher cortisol reactivity than the children with no aggression or proactive aggression. Moreover, in another study, Loney (Loney *et al.* 2003) found that low basal cortisol levels were correlated with *callous unemotional traits* (cf. non-explosive)in male adolescents, but a similar relationship was not observed in female adolescents. Comparing to the results of another study some researchers have found that salivary cortisol was reduced in children with attention deficit/hyperactivity disorder combined with oppositional defiant disorder (Kariyawasam *et al.* 2002).

3. Existence of subtypes/classes of aggression

Another factor that is not always taken into consideration is the existence of subtypes/classes of aggression. While some of the subtypes can be connected to higher levels of testosterone, others may not (Tordjman *et al.* 1997). Limitations in exact evaluation of aggressive symptoms do not allow precise objective classification of subtypes of aggressive behavior, thus aggressive behavior of probands in studies are heterogeneous and findings about relationships between testosterone and aggression may not be exposed. A similar problem was noted in the treatment of self-injuries behavior (SIB) in children with intellectual disabilities with the opiate antagonist-naltrexone. While some researchers found that SIB was decreased after treatment with naltrexone (Thompson *et al.* 1994), some described little effect (Winchel & Stanley 1991). Afterwards various subtypes of SIB responding to different medications have been described, among them one subtype, extreme self-inflicted injury, caused by partial analgesia of patients with congenital altered central pain mechanism and this type of SIB was the most responsive to treatment with opiate antagonists (e.g. naltrexone) (Mace & Mauk 1995).

4. Methods of measurement of aggression

Among the main limitations of most studies conducted in order to determine the relationship between testosterone levels and aggression in humans are the methods of measurement of aggressive symptoms. These measurements are based on subjective evaluation in scales/inventories completed by tested individuals or on rankings provided by caregivers/parents e.g. (Campbell *et al.* 1997; Anderson *et al.* 1992; Barzman *et al.* 2013; Dabbs *et al.* 1987; Dmitrieva *et al.* 2001; Golubchik *et al.* 2009; Scerbo & Kolko 1994; van Goozen *et al.* 1998; Yu & Shi 2009; Constantino *et al.* 1993). Assessment of aggressive behavior based on experimental design during functional behavioral analysis may be useful for future research in order to obtain objective and quantitative characteristics such as function, frequency, intensity, and duration of aggressive episodes (Iwata *et al.* 1994). These characteristics could be correlated with plasmatic testosterone levels (and other components of androgen activity, as well as other hormones) and thus define more specifically the relationships between this hormone and behavior. Moreover during functional behavioral analysis, some biological characteristics (such as arousal- high involvement of autonomic nervous system) can be measured helping to classify possible aggression subtypes (e.g. explosive aggression) (Lopez-Duran *et al.* 2009; Tordjman *et al.* 1997).

C. Hyperandrogeny related to higher arousal and explosivity

Increased physiological arousal manifested as higher sympathetic tone/arousal has been found to be related to explosive aggression in children and adults in many studies (Scarpa *et al.* 2010; Xu *et al.* 2014). Some of the researchers suggest that measurement of levels of physiological arousal in individuals could be an indicator of explosive aggression and might be used in a differential diagnosis of aggression subtypes in the future (Kempes *et al.* 2005; Xu *et al.* 2014).

1. Physiologiocal arousal as an indicator of explosivity

Heart rate variability (HRV) is the physiological phenomenon of variation in the time interval between heart beats. It is used as indices of physiological arousal and it shows regulation of cardiac activity by the autonomic nervous system. Values of HRV can describe the balance between parasympathetic and sympathetic divisions of the autonomic nervous system. Usually, high values of HRV at rest determine the domination of the parasympathetic division (higher vagal tone) which is related to mental and physical health. On the other hand reduced HRV has been shown to be associated with lots of medical conditions (Ellis & Thayer 2010). In a recent study reactive aggression (cf. explosive) was significantly related to decreased HRV while proactive aggression (cf. non-explosive) was significantly related to increased HRV (Scarpa *et al.* 2010). Moreover, lower vagal tone (parasympathetic division) was directly related to higher reactive but not proactive aggression in children in another study (Xu *et al.* 2014).

2. Testosterone activity and physiological arousal

An excess of androgens is known to be related to increased sympathetic tone in female mice (Nohara *et al.* 2013) which is generally correlated with decreased heart rate variability and thus to increased arousal. Another study found that women with polycystic ovary syndrome (hyperandrogeny medical condition) have increased sympathetic tone (Sverrisdottir *et al.* 2008). A study found out that the cardiac modulatory balance differs between genders and is characterized by

a greater influence of the vagal component in women and by the sympathetic component in men (Dutra *et al.* 2013) which can indirectly implicate the role of testosterone in increasing arousal/explosivity.

D. Potential anti-androgen therapy

Cyproterone acetate, medroxyprogesterone acetate, leuprolide acetate and spironolactone are anti-androgen drugs used when there are indications of hyperandrogeny. Their mechanism of action varies but the main effect is lowering the androgen effect of testosterone (either via lowering its production or via blocking its action). They are frequently used in the treatment of androgen dependent cancers, precocious puberty, hirsutism, acne, and other conditions (Goodman *et al.* 2011). These medications have also been used in the treatment of aggression in various clinical populations: sexual offenders, demented aggressive patients, aggressive patients with brain injuries, children with precocious puberty, and children with ASD (Bradstreet *et al.* 2007; Caparros-Lefebvre & Dewailly 2005; Huertas *et al.* 2007; Laue & Cutler 1994; Leschek *et al.* 1999; O'Connor & Baker 1983). Anti-androgen medication may prove a valuable adjunctive treatment to behavioral interventions and reduce the intensity and duration of aggressive episodes in individuals with explosive aggression and ASD.

Although existing evidence for the therapeutic effects of anti-androgen medication is promising, there are no randomized controlled trials with most research involving uncontrolled case studies or open trials conducted mainly in populations others than children with autism. Some reports are anecdotal findings of reduced aggression during primary treatment of other diseases with anti-androgen medication (e.g. precocious puberty) (Laue & Cutler 1994; Leschek *et al.* 1999). Important limitations of anti-androgen therapy are potential adverse side effects. Although anti-androgen therapy in children is not rare in cases of abnormally high plasmatic testosterone levels (in the indications of precocious puberty, congenital adrenal hyperplasia and hirsutism), potential adverse side effects with developing children are critical to consider. Research investigating hormonal levels in ASD children and objective assessment of aggressive behavior are essential for further potential clinical indications for anti-androgen therapy.

CONCLUSION

Till now only two studies focusing on androgen activity and aggression in children with ASD have been published (Tordjman *et al.* 1997; Pivovarciova *et al.* 2014), both differentiating subtypes of aggression (explosive/non-explosive). However in literature, there is some evidence linking testosterone to explosivity and aggression and lots of studies linking testosterone to aggression in general. There are several limitations in current research that need to be addressed in future investigation on relationship between testosterone and aggression in children with ASD and potential anti-androgen therapy: involvement of other components of androgen activity (e.g., function of enzymes responsible for metabolism of testosterone, sensitivity of androgen receptors, levels of active/free testosterone in plasma), involvement of other hormones in etiopathogenesis of aggression in humans (cortisol, oxytocin, serotonin and others), existence of subtypes/classes of aggression; and methods of evaluation of aggressive symptoms. Research investigating physiological arousal via measurement of heart rate variability in explosive type of aggression is also necessary in order to support objective differentiation of two aggression subtypes.

We believe this review provides background to warrant further pursuit of a biobehavioral model of aggression in children with ASD.

Conflicts of interest Statement

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