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Review

The role of trauma in the hormonal interplay of cortisol, testosterone, and oxytocin in adolescent aggression

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ABSTRACT

Although numerous studies have examined the neuroendocrinology of aggression, the findings are mixed and focused on cortisol and testosterone. We argue that past findings remain inconclusive partly because the key roles of oxytocin and trauma have not been systematically integrated yet. Oxytocin is associated with social behavior and interacts with cortisol and testosterone, whereas trauma is a crucial risk factor of aggression that strongly affects hormonal activity. In this review, we investigate the role of trauma in the hormonal interplay of cortisol, testosterone, and oxytocin in aggression during adolescence. We first discuss how these hormones interact with each other and how trauma influences these interactions and then we propose a model that highlights the role of trauma in the hormonal interplay in aggression. We suggest that the timing of trauma has a distinct effect on hormonal activity and it should be integrated into any comprehensive model. Current trauma is linked to different levels of oxytocin, cortisol, testosterone, and testosterone/cortisol ratio than childhood trauma, but this distinction is also influenced by gender and type of aggression. We conclude that in order to better understand the neuroendocrinology of aggression, it is crucial to incorporate the investigation of oxytocin and trauma in future research.

1. Introduction

Cumulative scientific evidence has shown that aggressive behavior is linked to abnormal hormonal levels, most notably lower levels of cortisol and higher levels of testosterone (Yildirim and Derksen, 2012a,b). However, empirical findings have also shown conflicting relations, depending on additional other factors including type of aggression, age, the presence of callous-unemotional (CU) traits, and methodological variations (Barzman et al., 2010; Cima et al., 2008; Gao et al., 2009; Herpers et al., 2014). This line of research has provided insight into the psychophysiology of aggression, but it suffers from several shortcomings.

The most notable problem is the conceptual complexity of aggression. Aggression is an umbrella term that generally refers to behaviors that aim to cause physical or psychological pain/harm to another individual or destruction/damage of an entity, but the construct of aggression is far more complicated (Tremblay et al., 2005). Aggression comprises a plethora of different types, including overt and covert aggression, reactive and proactive aggression, impulsive aggression, delinquent behavior, pathological forms of aggression, like oppositional-defiant disorder (ODD), conduct disorder (CD), antisocial personality disorder, and psychopathy or CU traits (APA, 2013; Tremblay et al., 2005). These different types play a key role in the inconsistent findings and incomparability among studies. In addition, research has mainly focused on cortisol and testosterone, ignoring the potential role of oxytocin, a neuropeptide that is strongly associated with social-affective behaviors. Moreover, the variables that have been investigated in order to elucidate the conflicting findings were limited and did not systematically include crucial and complex factors that are consistently related to both aggression and hormonal activity, most importantly, history of trauma.

To elaborate on the first issue, oxytocin is a neuropeptide that has been widely investigated for its role in social-affective behaviors, including social affiliation, pair bonding, emotional recognition, trust, empathy, and attachment, all of which are impaired in aggressive individuals (Campbell, 2008, 2010; Lee et al., 2009a; Veening and Olivier, 2013). Oxytocin is also related to cortisol and testosterone in several social behaviors. Specifically, even though cortisol is the most commonly examined stress hormone, oxytocin is also altered under physiological and psychological stressors, both in plasma concentrations and several brain regions (animals: Engelmann et al., 2004; Neumann, 2002; humans: Lee et al., 2009a). The release of oxytocin leads to the decrease of cortisol levels in order to reduce stress (Cardoso et al., 2014). Additionally, oxytocin has the opposite effects of

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testosterone on the same cognitive and behavioral phenotypes, such as threat response, empathy, and trust (Crespi, 2016). For instance, testosterone administration reduces empathy and trust, whereas oxytocin administration reinforces these behaviors (Crespi, 2016). We argue that oxytocin, in interaction with cortisol and testosterone, also plays a pivotal role in regulating aggressive behavior.

With respect to the role of trauma, previous studies have not systematically taken into account the potential role of trauma in relation to abnormal hormonal activity in aggressive individuals. Childhood trauma is predictive of persistent aggression and offending and antisocial adolescents have usually experienced multiple traumas, such as loss and bereavement, domestic violence, physical and emotional maltreatment, abuse, and neglect (Dierkhising et al., 2013; Fox et al., 2015; Foy et al., 2012; Jonson-Reid et al., 2010; Kotch et al., 2008; Steiner et al., 2011; Wilson et al., 2009). Additionally, hormone production and secretion are substantially influenced by early social experiences long before the manifestation of aggressive behavior. It has been proposed that early negative social experiences change sensitivity to neuropeptides and steroids by reorganization of receptors or alterations in hormone production and secretion that in turn influence social behaviors (Cushing and Kramer, 2005). In humans, trauma is a multifaceted construct with acute and chronic effects that lead to distinct alterations in the brain and the neuroendocrine systems (Cushing and Kramer, 2005; Teicher et al., 2003). Therefore, the hormonal alterations caused by trauma might interfere with the unique neuroendocrine profile of aggression leading to the observed conflicting findings. In sum, traumatic experiences are of paramount importance in our effort to disentangle the psychophysiology of aggression not only due to their high prevalence rates in antisocial and delinquent individuals but also due to their effect on hormonal activity.

The aim of this review is to address these issues and present a model based on the neuroendocrine findings of the hormonal interplay between cortisol, testosterone, and oxytocin as well as their relation to trauma. First, a brief description of the endocrinological changes in adolescence and the relation of cortisol and testosterone with aggression are presented. Since previous reviews and meta-analyses have already thoroughly discussed this topic and the aim of the current review is to focus on the interplay among these hormones and the role of trauma, it is outside the scope of this review to repeat the findings of the separate effects of these hormones in detail (e.g., Hawes et al., 2009; Yildirim and Derksen, 2012a, 2012b). Second, we review in more detail the evidence on the association between oxytocin and aggression. Third, we discuss in detail the interactions among these hormones followed by their association with trauma. Due to the limited number of studies examining the interaction among all three hormones, we also include studies that focused on the interaction between two of the three hormones. We finally integrate previous findings in a model presenting how the presence and timing of trauma influences the hormonal interplay of these hormones in aggression. The model is followed by a critical discussion of its strengths, limitations, and clinical relevance. We focus on findings in adolescence, because it is a unique developmental period with significant hormonal and maturational changes as well as high prevalent rates of aggression (Bramen et al., 2011; Merikangas et al., 2010; Shirtcliff et al., 2012; Shirtcliff et al., 2009a).

Given the scarce evidence on the relation between oxytocin and aggression or trauma in adolescence, we also discuss adult and children studies for oxytocin in an effort to shed light on its hormonal activity and interplay. Finally, several types of aggression have been examined in relation to hormonal secretion but due to the limited research on the specific hormonal interactions under investigation, we included studies that examined various types of aggression and we did not focus on one explicit type of aggression. Specifically, we included conduct disorder, antisocial personality disorder, offending, psychopathy, and aggression provocation in healthy samples. We also included Attention-Deficit Hyperactivity Disorder (ADHD) due to the impulsive aggressive outbursts often observed in youth with ADHD as well as the high comorbidity with conduct disorder (APA, 2013). As described above, these types have conceptual and behavioural differences and distinct characteristics, which might lead to distinct neuroendocrine profiles that will be taken into account in the model.

Although the aim of this review is to focus on the hormonal interplay in relation to trauma, there are several other factors that are associated with aggression and might influence its neuroendocrine profile that need to be acknowledged. For instance, alcohol and drug use is a well-known risk factor of aggression and delinquency (Assink et al., 2015; Hoaken and Stewart, 2003; Lundholm et al., 2013) and substance use disorders are often comorbid with antisocial personality disorder (Hasin and Kilcoyne, 2012). Relatedly, externalizing problems in adolescence are usually accompanied with symptoms of anxiety and depression (Hill, 2002). Despite its indisputable importance, the role of comorbidity in the neuroendocrine profile of aggression in relation to trauma is outside of the scope of this review as previous research examining all the aforementioned factors is considerably scarce.

2. Endocrine changes in adolescence

Adolescence is a unique developmental period characterized by substantial neurobiological, physiological, and psychological changes. In relation to the endocrine system, hormonal changes in the Hypothalamic-Pituitary-Adrenal (HPA) axis and the Hypothalamic-Pituitary-Gonadal (HPG) occur during puberty in adolescence (Gunnar and Vazquez, 2015; Shirtcliff et al., 2012; Shirtcliff et al., 2009a,b). Previous research has shown that HPA activity increases in adolescence with higher vulnerability to stressors and increased cortisol levels (Gunnar and Vazquez, 2015). Evidence on cortisol secretion has indicated an increase in basal cortisol levels from childhood to adolescence, although this pattern is not supported by studies on 24-h cortisol production, suggesting that changes in diurnal patterns might be in place (see for a review: Gunnar and Vazquez, 2015). A longitudinal study followed the diurnal cortisol patterns in 357 participants from the age of 9 until the age of 15 and found that morning cortisol declined over age, whereas afternoon and evening cortisol increased through adolescence with a peak at 15, leading to a flatter slope and higher daily cortisol output (Shirtcliff et al., 2012).

In parallel, the activity of the Hypothalamus-Pituitary-Gonadal (HPG) axis increases during puberty and leads to the secretion of steroid hormones, especially estradiol in females and testosterone in males in order to facilitate the development of adult anatomy and reproductive maturity (Guyton and Hall, 2006). This process begins with the secretion of the gonadotropin-releasing hormone (GnRH) from the hypothalamus, the secretion of which is largely inhibited during childhood (Guyton and Hall, 2006). Testosterone levels have been found to increase during puberty in both boys and girls aged 8–14 (Matchock et al., 2007). Taking into account the increased activation of the HPA and HPG during adolescence, a positive coupling between them is observed (Marceau et al., 2015; Marceau et al., 2014; Ruttle et al., 2015; Shirtcliff et al., 2015). Evidence suggests that this positive coupling begins at age 11 and gradually becomes more negative until the age of 15 (Ruttle et al., 2015). In contrast, during adulthood activation of HPA suppresses the activity of HPG and hence high cortisol is related to lower testosterone (Romeo, 2003; Stratakis and Chrousos, 1995; Terburg et al., 2009).

Furthermore, oxytocin can be detected as early as 14 weeks and reaches adult-like levels of immunoreactive cell number in the paraventricular nucleus by 26 weeks gestation (Hammock, 2015). Nevertheless, oxytocin-producing cells develop further postnatally. Evidence from animal studies suggests that maternal stimulation and grooming influence oxytocin receptor binding and HPA reactivity (Champagne et al., 2001; Francis et al., 2002). To date, there are no studies investigating the developmental pattern of oxytocin secretion in humans. One study examined cortisol and oxytocin levels in stress responses in 9–10 year olds and 15–16 year olds (Doom et al., 2016) and found that