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Short Communication

Lack of association between severity of ADHD symptoms and salivary oxytocin levels

Dennis Boyle[a], Orit Levi-Shachar[a,b], Hila Z. Gvirts[c], Orna Zagoory-Sharon[d], Ruth Feldman[d], Yuval Bloch[a,b], Uriel Nitzan[a,b], Hagai Maoz[a,b,*]

[a] Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[b] Shalvata Mental Health Center, Hod-Hasharon, Israel
[c] Department of Behavioral Sciences and Psychology, Ariel University, Ariel, Israel
[d] Baruch Ivcher School of Psychology, Interdisciplinary Center, Herzlia, Israel

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ABSTRACT

Impairments in the reactivity of Oxytocin (OT) system were associated with interpersonal difficulties in children with ADHD. The current study aimed to explore the correlation between symptoms severity and salivary OT levels at different time-points in children with ADHD. Symptoms severity was assessed in 50 children with ADHD (28 males, mean age 9.42 ± 1.65) using the Swanson, Nolan and Pelham Questionnaire-IV (SNAP-IV) and the Strengths and Difficulties Questionnaire (SDQ). Salivary OT levels were measured at baseline, as well as 15 min after positive social interaction. There was no statistical correlation between severity of ADHD and salivary OT levels in each of the time points. We conclude that impairments in the reactivity of the OT system in children with ADHD, associated with interpersonal impairments, might be a distinct aspect of the clinical picture, differentiated from the levels of inattentive, hyperactive/impulsive or behavioral symptoms.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is amongst the most common childhood disorders, with a prevalence of 5.3% in school-age children (Posner et al., 2020). In addition to the classic symptoms of inattention, impulsivity and/or hyperactivity, children with ADHD also suffer from impaired social functioning as compared to their healthy counterparts (Posner et al., 2020). This impaired social functioning can be considered an independent risk factor for the behavioral and interpersonal problems seen in these patients (Uekerman et al., 2010).

Impairments in Theory of Mind (ToM) were associated with poorer interpersonal relationships in children with ADHD (Uekerman et al., 2010). Some studies also suggested that poor performance in ToM tasks correlates with ADHD severity, and that administration of methylphenidate in children with ADHD improve performance on ToM tasks to match the levels of their healthy peers (Maoz et al., 2014; Levi-Schachar et al., 2020).

Oxytocin (OT), a neuroendocrine peptide that is produced in the hypothalamus and released in the posterior pituitary, was found to play a role in mediating social cognition and functioning (Feldman, 2010). Among its numerous effects, OT has been shown to be important in social memory, attachment, bonding, and trust. The social salience hypothesis suggests that OT modifies responses to contextual social cues, but that its effects are dependent on numerous characteristics unique to each individual, such as personality traits and presence of psychiatric disorders (Shamay-Tsoory and Abu-Akel, 2016).

Dopamine (DA) has been demonstrated to have an intricate linkage with OT, having anatomically proximal neurons and receptors on some of the same neurons (Baskerville and Douglas, 2010). Crosstalk between OT and DA has been posited to integrate reward with social interaction, thus playing a central role in mediating and encouraging human social behavior (Baskerville and Douglas, 2010: Feldman, 2017). Given that DA transporter and receptor abnormalities are amongst the most important causes of ADHD, it was suggested that OT also plays a role in the pathophysiology of ADHD, especially in mediating social deficits (Wu et al., 2012).

Two previous studies have related ADHD symptom severity and serum OT levels (Sasaki et al., 2015; Demirci et al., 2016). These studies have shown a negative correlation between serum OT levels and ADHD scores, and a positive correlation between serum OT levels and empathy

* Corresponding author at: Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.
E-mail addresses: hagaima@gmail.com, hagaima@clalit.org.il (H. Maoz).

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scores. Importantly, however, both studies measured OT only at baseline and not after a social interaction. This is notable because the OT system is reactive to environmental stimuli, like interpersonal interactions. In a previous study we showed that as oppose to healthy controls (HCs), salivary OT levels of children with ADHD does not increase in response to positive interpersonal experience. However, administration of MPH in these children normalized their post-interaction OT levels to match those of the HCs (Levi-Schachar et al., 2020). These results implicate that impairments in the reactivity of the OT system might serve as a possible mediator of social deficits in children with ADHD and, further, demonstrate a possible mechanism by which stimulants improve social functioning in children with ADHD.

In the current study we aimed to assess whether, in children with ADHD, there is a correlation between the symptoms severity and the impairment in the OT system.

2. Methods

2.1. Subjects

Subjects included in this study were part of the previously reported study, which aimed to assess the influence of MPH on the reactivity of the OT system in children with ADHD and in HCs. The methods employed in this study are described in detail in prior publications (Levi-Schachar et al., 2020). Fifty children (28 males), aged 6–12, diagnosed with ADHD, were recruited. Patients were recruited from the ADHD clinic of the Shalvata Mental Health Center, School of Medicine, Tel-Aviv University. ADHD was diagnosed by child and adolescent psychiatrists using the Diagnostic and Statistical Manual of Mental Disorders, fourth or fifth edition (DSM-IV-TR and DSM-5). We excluded children with a past or current affective disorder, psychosis, substance abuse, conduct disorder or any medical or neurological condition or medication use that might affect the child's participation in the study. We also excluded children who had a first-degree relative with a major psychiatric diagnosis. The study was approved by the institutional IRB. Both parents of each participant signed a consent form, and each child gave consent verbally.

2.2. Procedure

Apart from the initial clinical assessment at the clinic, all assessments were performed in the children's homes. Children participated in two sessions, in a randomly assigned order: one session an hour after taking short-acting MPH, and one session an hour after taking a placebo. We report here only the relevant results concerning ADHD patients in the placebo condition. Parents completed questionnaires regarding demographics and general information about each of their children's academic and social functioning. In addition, parents completed the Swanson, Nolan and Pelham Questionnaire-IV (SNAP-IV) (Swanson et al., 2001), which subscales 18 ADHD and 8 oppositional defiant disorder (ODD) symptoms specified in the DSM-IV. Symptoms are scored on 4-point Likert-scale (from 0 = not at all to 3 = very much). Subscale scores are calculated by averaging the item scores within the domains of Inattention, Hyperactivity/Impulsivity, and Opposition/Defiance. Parents also filled out the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997), a screening inventory composed of five distinct dimensions: conduct problems, emotional symptoms, hyperactivity, peer problems, and pro-social behavior. Each of the scales contains five items that scores between 0 ("not true") and 2 ("certainly true"). Accordingly, for each of the scales, the score can range from 0 to 10.

During each session, salivary OT levels were measured at three time points: at the beginning of the session ("T1"), 40 min after the administration of MPH/PLC, (in order to assess the effect of MPH/PLC on OT levels, regardless of social interaction ("T2")), and following interpersonal interaction ("T3"). In the current analysis, since only PLC was given to patients, and in order to strengthen the validity of the measurements of OT levels, we calculated the mean salivary OT levels of T1 + T2. Studies show that changes in central salivary OT levels are best reflected in peripheral OT measurements taken 15 min later (Feldman, 2012). Hence, the third measurement ("T3") was set to 15 min after a "positive social interaction" in which the child and the parent were asked to plan a "fun day" that would include both of them, and to talk about it for five minutes (Feldman, 2012). Participants were asked to avoid drinking and eating an hour before the test and to avoid caffeine three hours before the test.

Saliva samples were collected by passive drool into designated tubes at each of the three time points. In order to precipitate the mucus, samples underwent four freeze-thaw cycles: freeze at − 70 °C and thaw at 4 °C. After the fourth cycle the tubes were centrifuged twice at 4000 rpm for 30 min. Supernatants were collected and stored at − 20 °C until assayed. Determination of OT from saliva samples was performed using OT ELISA kit (Enzo Life Sciences, NY, USA). Measurements were performed in duplicate according to the manufacturer's instructions. The concentrations of samples were calculated using MatLab-7, according to relevant standard curves.

2.3. Statistical analysis

The complete statistics of the current study is described in detail elsewhere (Levi-Schachar et al., 2020). For the purpose of the current study, Pearson correlations were used to assess correlations between salivary OT levels and SNAP and SDQ scores. Significance level was set at 0.05.

3. Results

Table 1 presents demographic and clinical parameters. The mean age of patients was 9.42 ± 1.65. The mean score for inattention was 2.19 ± 0.84, for hyperactive/impulsive symptoms 1.99 ± 0.78, and for oppositional symptoms 2.02 ± 0.80.

The mean salivary OT level at T1 and T2 was 35.24 ± 30.31 pg/mL. Following positive interpersonal interaction (T3), the mean salivary OT level decreased to 26.86 ± 18.69 pg/mL. There were no significant correlations between ADHD symptom severity, as measured by each of the SNAP-IV and SDQ subscales, and salivary OT levels, both at baseline and following positive interpersonal interaction.

4. Discussion

The purpose of the current study was to evaluate whether the degree of impairment of reactivity of the OT system is correlated with symptom severity in children with ADHD. As reflected by the SNAP-IV and SDQ reports, the children in this study had moderate symptom severity.

In a previous report (Levi-Schachar et al., 2020), we showed that in

Table 1
Demographic and clinical characteristics of ADHD patients (n = 50).

Parameter	Mean score
Age, years	9.42 ± 1.65
Number of siblings	2.04 ± 0.91
SDQ, emotional distress	3.65 ± 2.57
SDQ, behavioral difficulties	3.1 ± 2.18
SDQ, hyperactivity	5.93 ± 2.82
SDQ, social difficulties	2.38 ± 2.26
SDQ, pro-social	7.14 ± 1.91
SNAP, inattention	2.19 ± 0.84
SNAP, hyperactivity/impulsivity	1.99 ± 0.78
SNAP, oppositional	2.02 ± 0.80
Salivary OT level – mean T1/T2	35.24 ± 30.31
Salivary OT level – T3	26.86 ± 18.69

SDQ = Strengths and Difficulties Questionnaire; SNAP = Swanson, Nolan and Pelham Questionnaire-IV; OT-oxytocin; T1 = baseline; T2 = 40 min after administration of placebo; T3 = following interpersonal interaction.

children with ADHD, in comparison to HCs, salivary OT levels tend to decrease, instead of increase, following positive social interaction. This finding may imply that, at least in part, some of the social difficulties known to affect children with ADHD, might be related to impairment of the OT system. Other studies have also noted impairment in the OT system in children with ADHD. For example, one study found that serum OT levels in pediatric patients with ADHD were significantly lower than the levels in matched controls. Moreover, that study found that serum OT levels in medicated patients with ADHD were significantly higher than in unmedicated patients with ADHD (Sasaki et al., 2015).

Impairment in the DA system, has repeatedly been implicated as amongst the most important etiological factors in patients with ADHD (Wu et al., 2012). Fittingly, most of the drugs approved for ADHD treatment (e.g., methylphenidate and amphetamine), work by altering DA signaling in the brain. It has been established that OT and mesolimbic dopaminergic neurons are reciprocally connected. Anatomical and immunocytochemical studies have revealed that the receptor binding sites and neuronal fibers of these two neuroregulators exist in adjacent CNS regions, often in apposition to each other (Baskerville and Douglas, 2010). Moreover, hypothalamic OT cells express dopamine receptors, suggesting direct regulation. There is also evidence for the existence of dopamine d2-OT receptor heteromers in the ventral and dorsal striatum with receptor-receptor interactions (Romero-Fernandez et al., 2012).

Numerous studies have also noted the relationship between OT and DA in the context of the limbic system, with some suggesting that in humans, OT, like DA, plays a prominent role in that system, including in the anterior cingulate cortex and the amygdala (Sasaki et al.,2015). It is likely that ADHD therapy, in addition to modulating DA signaling, also affects OT regulation in the limbic system (Sasaki et al., 2015).

The results of the current study showed no significant correlations between symptom severity and salivary OT levels, both at baseline and following positive social interaction. Further analysis showed no correlation between symptom severity and the difference in OT levels between baseline and following social interaction. While impairment in the OT system is unlikely to be quantitatively related to symptom severity, it is likely that impairment in the OT system plays a role in the greater picture of pathophysiology of ADHD, and especially the social and interpersonal impairments. Identifying OT dysregulation as a likely independent moderator of interpersonal impairments in children with ADHD, not directly correlated with the level of inattentive or hyperactive/impulsive symptomatology might aid clarify some of social impairments that characterize this disorder.

5. Limitations

The findings of the current study should be viewed considering several limitations. First, given the need for high ecological validity, we performed the study in the children's homes. Hence, results might have been affected by "non-sterile" conditions. Also, though children were instructed not to eat or drink an hour before the examination, we could not ensure that they indeed avoided eating or drinking, which might affect OT levels. Lastly, OT levels were measured in the saliva and not in the CNS. However, previous studies assessing the extent to which salivary and central (i.e., CNS) OT concentrations are correlated show that OT concentrations in the saliva better correlate with OT concentrations in the cerebrospinal fluid than blood OT concentration (Valstad et al., 2017).

Conflict of interest

The authors have no conflict of interest to report.

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