Sex-specific Effect of Intranasal Vasopressin, but not Oxytocin, on Emotional Recognition and Perception in Schizophrenia Patients

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ABSTRACT

Background: Impairments in social behavior and cognition, such as the ability to identify others’ emotional state, are important features in schizophrenia. Arginine vasopressin (AVP) and oxytocin (OXT) are nonapeptides that influence social cognition and behavior. Previous studies have shown that the administration of intranasal AVP or OXT may affect the ability to recognize facial emotions and that the effects of intranasal AVP administration are sex specific. The primary objective of this study was to investigate the effects of a single dose of AVP or OXT on social cognition in patients with schizophrenia. The secondary objective of the study was to test for sex-specific effects of intranasal AVP and OXT administration on social cognition.

Methods: In this double-blind, placebo-control, crossover study, 34 patients diagnosed with schizophrenia or schizoaffective disorder received a dose of AVP, OXT or placebo in three separate meetings. Forty-five minutes after administration, subjects performed three facial emotion recognition tasks, “Reading Mind in the Eyes” Test (RMET), the Face Emotion Identification Test (FACE-ID) and the Face Emotion Discrimination Test (FACE-DISCRIM). Thirty subjects completed all sessions and only their data were analyzed.

Results: There were no significant main effects of hormone administration on the ability to recognize facial emotions between treatment conditions. However, AVP administration resulted in sex specific differences in emotion recognition in the FACE-ID task. Specifically, in men, AVP administration reduced the ability to recognize angry faces. In women, AVP administration reduced the ability to recognize sad faces and improved the ability to recognize fearful faces.

Conclusions: These findings indicate that intranasal AVP may affect the recognition of facial emotions differently in men and women. Thus, AVP may increase the differences between men and women on social cognition.

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INTRODUCTION

Social impairments are considered a hallmark of schizophrenia (1) and have important implications for the development, course, and outcome of the disorder (2). Social impairments in schizophrenia include not only deficits in social functioning, but also deficits in social cognition. Facial emotion recognition (FER) is an important component in social cognition and is essential to guide social functioning and behavior (3). Patients with schizophrenia have deficits in recognizing different aspects of facial information (4), such as identity matching/discrimination tasks and familiarity recognition tasks (5, 6), even from the initial visual stages (3). Impairments in FER are typically present before the onset of full-blown psychosis and remain stable over the course of illness (7), and deeply affect individuals’ social functioning and interpersonal relationships (8). Thus, understanding the biological factors of FER in schizophrenia may play a crucial role in understanding the etiology of the disorder and in developing interventions that improve patients’ quality of life.

Vasopressin (AVP) and oxytocin (OXT) are neurohypophyseal hormones that coordinate both the causes and consequences of social interactions, primarily through the action of their receptors (9). Decades of research have characterized their well-known peripheral effects (AVP on water resorption and vasoconstriction, OXT on uterine contraction and lactation). More recent research into the central effects of these neuropeptides has identified them as paramount regulators of social cognition and behavior (10, 11). In particular, studies employing intranasal administration of the hormones, which presumably allows for delivery of the hormone to the brain, demonstrate marked changes in social perception and behavior (12-23).

In non-clinical populations, intranasal administration of OXT improves recognition of basic emotions, suggesting a potential pharmaceutical target for psychopathologies characterized by deficits in social interactions such as autism spectrum disorders, social anxiety disorders, and schizophrenia. Clinical research examining the effects of OXT in schizophrenia is still in its infancy, however some studies point to potential therapeutic effects (24-28). For example, Goldman et al. (29) found that emotion recognition was improved by a single administration of 20IU intranasal oxytocin to schizophrenia patient with polydipsia but did not effect non-polydipsic patients or when given in low doses (i.e., 10IU). Averbeck et al. (30) also found that a single administration of intranasal OXT (24IU) improves emotions recognition in schizophrenia patients. Moreover, studies employing chronic intranasal OXT administration for several weeks found evidence for reduced symptoms (25), improved social perception (26) and improved verbal memory in schizophrenia patients (27). Davis et al. (31) found that a single high dose (40 IU) administration of intranasal OXT may improve performance in high level cognitive tasks in schizophrenia.

However, it did not significantly effect social cognition composite score. Another study by Davis et al. (28) showed that administration of intranasal OXT for six weeks before social cognitive training improved schizophrenia patients’ ability at high level social cognition (e.g., empathy), but not in other social cognitive tests (e.g., facial affect recognition).

In non-clinical populations, intranasal AVP studies show inconsistent results. Guastella et al. (19) reported that intranasal AVP enhances the encoding, but not the recognition, of happy and angry faces in men. Uzefovsky et al. (20) found that intranasal AVP administration selectively impaired the recognition of negative emotions in men, but Kenyon et al. (21) found no such effect. Importantly, Thompson et al. (32) found that effects of intranasal AVP administration are sex specific. Specifically, in men, AVP facilitated agonistic facial motor patterns and decreased perceptions of friendliness in unfamiliar faces. In women, the opposite effect was found: AVP facilitated affiliative facial motor patterns and increased perceptions of friendliness. Less research has been conducted examining the effects of AVP in emotion recognition in schizophrenia, however, here too, preliminary studies show some promise (33).

In light of previous research, we hypothesized that intranasal administration of OXT or AVP may improve emotion recognition in patients with schizophrenia and suggest to examine it in three different tasks that required different abilities from the subject. Since previous research has also pointed to sex-specific effects, we also examined whether there are sex differences in emotion recognition after OXT and AVP administration.

MATERIAL AND METHODS

SUBJECTS

Thirty-four patients from the Psychiatry Department and outpatient clinic at the Afula Medical Center with a diagnosis of schizophrenia or schizo-affective disorder were recruited for this double-blind, placebo-controlled, crossover study. Psychiatric diagnoses were confirmed by a master-level clinician using DSM-IV-TR criteria (34). All participants were stabilized on antipsychotic medication and none had a history of substance abuse or...
head injury. The study was approved by the IRB at Afula Medical Center and by the Israel Ministry of Health.

**PROCEDURES**

At the first meeting all participants provided written informed consent after receiving an oral explanation and being assessed by a senior psychiatrist using the Positive and Negative Syndrome Scale (PANSS) (35). Participants were then randomized into three groups (counterbalanced for AVP, OXT, and placebo treatment order), and asked to return for three additional monthly visits. All subjects received one dose of treatment (24 IU) of OXT (diluted in 0.9% NaCl Sigma, Germany)/24IU of AVP (diluted in 0.9% NaCl Sigma, Germany)/placebo (sterile saline, 0.9% NaCl), a different substance at each visit, and the emotion recognition tasks were administered after a 45-minute waiting period.

**INSTRUMENTS**

Three tests of emotion recognition were employed, all presented on the same 19” computer monitor: “Reading Mind in the Eyes” Test (RMET), the Face Emotion Identification Test (FACE-ID) and the Face Emotion Discrimination Test (FACE-DISCRIM).

The RMET (36) contains 36 pictures of the eye region. For each picture, each participant was asked to mark on a paper form one of four possible words that best describes the emotion displayed in the picture. The emotions presented were varied and reflected the complexity of the nuances of human emotions. The Face Emotion Identification Test (FACE-ID) and the Face Emotion Discrimination Test (FACE-DISCRIM) use black and white photographs of faces displaying different emotions (23). FACE-ID consists of 19 photographs of facial emotions presented for approximately 15 seconds with a blank screen of approximately 10 seconds between pictures. Participants were given a piece of paper on which six emotions were listed (happy, sad, surprised, fearful, angry and shy), and asked to look at each face and mark the word that best describes the emotion in the photograph. FACE-DISCRIM consists of 30 pairs of black and white facial photographs. Participants were asked to mark on a paper form whether the two faces in each pair displayed the same or different emotions. In all tasks, participants were asked to guess if unsure of the correct answer.

Within-subject analyses were performed to compare the differences in every task after all treatments (OXT, AVP and placebo) using repeated measure ANOVA (rmANOVA). Gender differences in face recognition were measured using ANOVA. All statistical analyses were performed using SPSS 15.0.

**RESULTS**

Four subjects withdrew their participation because of discomfort caused by the intranasal administration and did not complete the emotion recognition tasks. Thirty subjects (17 male, age 43.8±2.3, were screened and participated in all three study meetings. Seven subjects received a diagnosis of schizoaffective disorder and 23 of schizophrenia. Demographic data is presented in Table 1.

An rmANOVA comparing treatments (OXT, AVP and placebo) found no significant treatment effects on total RMET scores (F=2.2, p-value=0.16), total FACE-ID scores (F=0.8, p-value=0.43) or total FACE-DISCRIM scores (F=3.3, p-value=0.14).

No differences between males and females were found in age, PANSS positive, negative or total scores. However, differences between males and females were found in PANSS general scores (t=2.3, p-value= 0.034), and it was entered as a covariate in further analyses. Treatment x gender interactions were not significant in the RMET, FACE-ID or FACE-DISCRIM (all p-values>0.5) total scores. However, when examining gender and treatment interactions for emotion specific sub-scores in the FACE-ID significant differences emerged. Specifically, there was a significant interaction between treatment (AVP vs. placebo) and sex on recognition of fearful faces (F=3.4, p-value=0.042). Further examination of simple effects revealed that women improved recognition of fearful faces (F=6.5, p-value=0.025) after AVP administration as compared to placebo.

Furthermore, while the interaction between sex and treatment on angry faces did not obtain significance (p-value>0.05), a simple main effect analysis revealed that under the AVP condition men did less well than women at identifying angry (F=5.1, p-value=0.033) and

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Values are mean±SD for continuous variables and number of subjects for categorical values. PANSS, Positive and Negative Syndrome Scale.
fearful faces (F=4.9, p-value=0.036). Study results are presented in Tables 2 and 3.

**DISCUSSION**

The findings of this preliminary study support previous reports about the influence of intranasal AVP administration on the recognition of specific facial expressions\(^{20}\). We observed sex-specific influence of AVP administration on face recognition, which has also been previously reported (32). In this study, similarly to Uzefovsky et al. (20), a single administration of AVP reduced the recognition of angry faces in men. However, the same study was conducted on healthy men only and found this effect in the RMET task rather than what we found in the FACE-ID task which is a less complicated task. We also found that a single administration of AVP improved women’s ability to recognize fearful faces but decreased their ability to recognize sad faces. The literature suggests that there are gender differences in the genetic expression and the neurological structure of the AVP and OXT systems. In rats, there are sex differences in AVP projections from the bed nucleus of the stria terminalis and medial amygdaloid nucleus where there is a much higher AVP fiber density in males than in females from the second postnatal week (37).

Some clinical trials have shown that intranasal OXT significantly improves symptoms in schizophrenia patients and effect emotion recognition in both schizophrenia patients and healthy volunteers (14-16, 25-28, 30, 31, 38-40). Despite the encouraging findings, especially in the clinical trials by Feifel et al. (25, 27) and by Pedersen et al. (26), a meta-analysis by Bakermans-Kranenburg and van IJzendoorn (41) found no significant effects of OXT administration in schizophrenia. This may be due to lack of standardization and different methodology in the examined studies (e.g., different doses and length of administration, different domains of the disorder that were examined and small sample sizes). In the current study we also found no influence of intranasal OXT single administration on emotional recognition. This may be due to our study limitation (i.e., single dose administration of OXT and small sample size).

Fischer-Shofty et al. (40) found that single administration of intranasal OXT enhances fear but not happiness recognition in schizophrenia patients. The differences from our study may be as a result of larger sample size and mainly men in the Fischer-Shofty study. Although we did not find any effect of intranasal OXT administration, the fact that we found intranasal AVP to decrease fear recognition in men may point to the opposite effects of AVP and OXT.

The findings of our study together with previous studies suggest that in order to reduce symptoms in schizophrenia patients, hormones should be administered in high doses and for a long term. Moreover, this study emphasized the different effect of intranasal AVP between men and women. Therefore we recommend that future studies that deal with the effect of hormones take into consideration the gender effect. Further studies assessing gender effects following the chronic administration of intranasal hormones are essential to fully understand the potential of these treatments in disorders involving social deficits.
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Conflict of Interest
All authors report no financial conflicts for this article.

Contributors
RL, BB, RG, RPE and IK designed the study, BB and AR recruited the subjects, LV, IS and SI performed the emotion recognition assessment, RL and FU performed the statistical analyses, RL, RBM and BB wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

References