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# Peripheral vasopressin but not oxytocin relates to severity of acute psychosis in women with acutely-ill untreated first-episode psychosis

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ABSTRACT

*Background:* In women with chronic schizophrenia, higher levels of peripheral oxytocin have been associated with lower levels of positive but not negative symptoms. Sex-specific associations between endogenous levels of oxytocin (OT) and arginine vasopressin (AVP) with clinical symptoms and cognition in untreated early course patients have not been examined.
*Method:* Clinical ratings and neuropsychological testing were performed in thirty-eight acutely ill, unmedicated first-episode schizophrenia patients (14 women, 24 men). Serum hormone assays were obtained in patients and thirty-eight demographically similar healthy controls.
*Results:* Patients demonstrated increased AVP levels compared to controls ($p = 0.01$). Higher AVP levels were associated with greater positive symptoms ($r = 0.58$, $p = 0.03$) and worse verbal learning ($r = -0.63$, $p = 0.02$) in female, but not male, patients. OT levels did not statistically differ between patients and controls, and were unrelated to clinical symptoms or cognition in patients.
*Conclusion:* Results suggest an association of endogenous AVP with increased positive symptom severity and worse cognition in untreated female, but not male, schizophrenia patients. Findings support the role of neuroendocrine alterations in acute psychosis and the importance of examining sex-specific neuroendocrine alterations early in the course of schizophrenia.



## 1. Introduction

Sex differences in neuroendocrine factors may contribute to the clinical presentation and course of schizophrenia. Two sexually dimorphic neuropeptides, oxytocin (OT) and arginine vasopressin (AVP) — may particularly influence cognitive function and behavioral manifestations of schizophrenia. Previously, we reported sex-specific associations between peripheral OT, clinical symptoms, and emotion perception in chronic, medicated patients with schizophrenia (Rubin et al., 2010, 2011). In female, but not male, patients, higher peripheral OT levels were associated with less severe positive symptoms, less severe general psychopathology, and better emotion perception. It is unclear whether this reflects disease effects or the impact of antipsychotic medications on both OT and symptoms (Uvnas-Moberg et al., 1992; Kiss et al., 2009). Examining untreated, acutely ill, first-episode patients eliminates the potential confounding influence of chronic antipsychotic use, treatment responsiveness, and duration of illness effects.

OT is classically known for its role as a hormone involved in parturition and lactation. However, OT has wide reaching effects beyond reproductive behavior, and influences behaviors that are typically impaired in schizophrenia, including attachment, trust, stress management, social cognition, and memory (Fehm-Wolfsdorf and Born, 1991; Carter et al., 2008; Heinrichs et al., 2009). Animal and human studies suggest that abnormalities in OT may contribute to the clinical presentation of schizophrenia (for reviews, Feifel, 2011, 2012). In animal models of schizophrenia, haplo-insufficient reeler mice show reductions in OT receptors in regions of the hippocampus and retrosplenial and piriform cortex (Liu et al., 2005); which are critical areas for emotion, cognition, and positive symptoms in schizophrenia (Kuperberg and Heckers, 2000; Jardri et al., 2011). Although the direction is not always consistent, patients with schizophrenia have been shown to have altered central (Linkowski et al., 1984; Beckmann et al., 1985) and peripheral levels (Goldman et al., 2008; Keri et al., 2009) of OT in most but not all studies (Glovinsky et al., 1994; Rubin et al., 2010, 2011; Sasayama et al., 2012).

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Pharmacological studies administering exogenous OT to predominantly chronic male patients also suggest short-term benefits for positive and negative symptoms and social cognition (Feifel et al., 2010; Averbeck et al., 2011; Goldman et al., 2011; Pedersen et al., 2011). Mechanisms by which OT may have therapeutic effects on clinical symptoms could involve modulation of emotional regulation and the autonomic nervous system (Porges, 2001) and neurochemical systems dependent on dopamine and/or glutamate (Sarnyai and Kovacs, 1994; Feifel and Reza, 1999; Qi et al., 2008; Caldwell et al., 2009; Shahrokh et al., 2010; Rosenfeld et al., 2011).

OT interacts dynamically with a related neuropeptide, AVP. Both OT and AVP act within the central nervous system with effects on behavior and physiology (Landgraf and Neumann, 2004). Similar to OT, AVP is found in high concentrations in the paraventricular nucleus and the supraoptic nucleus of the hypothalamus and is transported to the posterior pituitary where it is released peripherally. AVP is classically known for its role in the kidney as a potent antidiuretic hormone (Weitzman and Kleeman, 1979). AVP is also released centrally during stressful experiences (Landgraf et al., 1998) and is implicated in the regulation of the hypothalamic-pituitary adrenal (HPA) axis, including cortisol secretion (Meyer-Lindenberg et al., 2011).

Changes in stress-related hormones such as AVP may be associated with the clinical symptoms and cognition observed in schizophrenia. Whereas OT influences stress management, cardiovascular regulation, and under some conditions may have amnestic effects on verbal learning and memory; AVP is more typically associated with vigilance, mobilization, increased reactivity to stressors, and improvements in verbal learning and memory (Strupp et al., 1983; Fehm-Wolfsdorf and Born, 1991; Carter, 1998; Carter et al., 2008; Ferris, 2008; Heinrichs et al., 2009; Gutkowska and Jankowski, 2012). Disruptions and interactions among these hormones may regulate physiology, behavior, and cognition allowing shifts between positive social behaviors and defensive states that are associated with the clinical symptoms of schizophrenia.

The purpose of the present study was two-fold. First, we aimed to compare the concentration of peripheral OT and AVP levels in unmedicated, acutely-ill first-episode schizophrenia patients to healthy controls. Second, we aimed to evaluate whether peripheral OT and AVP levels are associated with positive symptom severity and verbal learning in these patients. We hypothesized that OT levels would be decreased and AVP levels would be increased in patients compared to controls. We also predicted that OT would be associated with less severe positive symptoms and worse verbal learning, whereas AVP would be associated with more severe positive symptoms and possibly better verbal learning. Based on our earlier findings, we predicted that hormone associations with symptoms would be most pronounced in female patients.

## 2. Methods

### 2.1. Participants

The sample included 38 patients (14 women, 24 men; Table 1) recruited from the University of Illinois at Chicago (UIC) First-Episode Psychosis Program. Patients were between 16 and 50 years of age and had no known systemic, endocrine, or neurological disease. Of the 38 patients, 26 (68%) had no prior lifetime exposure to antipsychotic medications. The 12 patients with prior lifetime exposure to antipsychotic medications had prior treatment limited to less than eight weeks of cumulative exposure (median = 3.07 weeks). These antipsychotic medications were typically prescribed in the course of their illness prodrome or earlier during their first episode when they were initially seen by an emergency room or a community mental health center. These patients were antipsychotic free for at least 3 days (median time of washout = 5 days) at the time of the initial study assessments. Diagnoses were assigned according to Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria using the Structured Clinical Interview (SCID; First et al., 1995), along with collateral clinical data which were reviewed at consensus diagnosis meetings. Patients were diagnosed with either schizophrenia (n = 34; 90%) or schizoaffective disorder depressed type (n = 4; 10%).

A sample of 38 healthy controls (14 women, 24 men) were recruited from the community with no history of Axis I disorders based on the SCID or history among first-degree relatives of psychotic or mood disorders. Controls were comparable to patients on race and IQ but were slightly older than patients (28.0 vs. 24.4 years of age, $p<0.05$). No participants had history of head trauma with loss of consciousness for more than 10 min, neurological disorder, or lifetime history of alcohol or drug dependence. Two female patients and one female control were receiving oral contraceptives; including these women did not change the pattern of results.

**Table 1**
Baseline and clinical characteristics as a function of sex.

| | Patients | | Healthy controls | |
|---|---|---|---|---|
| Variables | Women (n = 14) | Men (n = 24) | Women (n = 14) | Men (n = 24) |
| Demographics | | | | |
| Age (years), M (SD)[G] | 26.93 (9.20) | 21.83 (5.30) | 28.43 (9.40) | 27.58 (3.26) |
| IQ, M (SD) | 97.00 (11.44) | 92.21 (13.69) | 99.00 (10.73) | 94.96 (30.96) |
| Race/Ethnicity (%) | 57% | 54% | 43% | 48% |
| African-American, non-Hispanic | 14% | 21% | 29% | 26% |
| Caucasian, non-Hispanic Hispanic | 14% | 21% | 21% | 13% |
| Other | 14% | 4% | 7% | 13% |
| Clinical variables | | | | |
| Consensus diagnosis (%) | | | | |
| Schizophrenia | 79% | 96% | | |
| Schizoaffective depressed type | 21% | 4% | | |
| No prior antipsychotic treatment (%) | 86% | 58% | | |
| Antipsychotic free at initial testing (%) | 100% | 100% | | |
| Treatment 48 h prior to testing (%) | | | | |
| Antidepressants | 7% | 0% | | |
| Mood stabilizer or stimulants | 0% | 0% | | |
| Benzodiazepines | 7% | 8% | | |
| PANSS, M (SD) | | | | |
| Positive subscale | 23.93 (5.59) | 24.50 (3.79) | | |
| Negative subscale | 19.50 (7.86) | 20.58 (4.97) | | |
| Hormone values, M (SD) | | | | |
| Oxytocin (pg/ml) | 349.09 (227.41) | 364.52 (257.03) | 342.98 (217.30) | 427.28 (259.01) |
| Vasopressin (pg/ml)[G] | 108.39 (89.85) | 109.63 (72.97) | 69.18 (25.86) | 74.10 (46.50) |

Note. [G] Main effect of group is $p<0.05$. PANSS = Positive and Negative Syndrome Scale.