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Relationship of Plasma Oxytocin Levels to Baseline Symptoms and Symptom Changes during Three Weeks of Daily Oxytocin Administration in People with Schizophrenia

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Abstract

Several clinical studies have found an inverse relationship between clinical symptoms and peripheral oxytocin (OT) levels in people with schizophrenia. As oxytocin is a putative treatment for schizophrenia, the effect of repeated dosing of OT on OT levels, clinical symptoms and the relationship between the two is of interest. In a, randomized, double blind, parallel group 3 week study (N=28) with daily administration of intranasal OT (20 IU twice daily) or placebo (PBO), we examined the effect of OT administration on the correlation between the change in peripheral OT levels and change in clinical symptoms in patients with schizophrenia. At baseline, there were no significant treatment group differences in OT levels. There were no significant associations between baseline OT levels and any symptom measures. After 3 weeks of OT/PBO dosing, there was no significant difference in the magnitude of change in OT levels between the two treatment groups. Correlations between changes in peripheral OT levels and changes in the BPRS total and

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CONFLICTS OF INTEREST

Dr. Kelly has served as an advisor for XOMA and Lundbeck, Dr. Buchanan served on the advisory boards for Amgen, Astellas, Janssen Pharmaceuticals, Inc., NuPathe, Inc., Pfizer, Roche, and Takeda. He also serves as a DSMB member for Pfizer and Otsuka. Dr. McMahon served as a consultant for Amgen. Other authors have no conflicts of interest to report.

CONTRIBUTORS

MRL, DLK, and HJW designed the study and wrote the protocol. MRL and DLK managed the literature searches and analyses. FL and RPM undertook the statistical analysis, and DLK wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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negative symptom scores were not different between treatment groups. Larger studies are needed to examine the effect of exogenous OT on peripheral OT levels and the relationship between the latter and clinical symptoms.

Clinical Trials.gov = NCT00884897

Keywords

oxytocin; schizophrenia; negative symptoms; oxytocin levels; positive symptoms; intranasal

1. Introduction

Early clinical trials of intranasal oxytocin (OT) in individuals with schizophrenia (SZ) suggest short-term benefits for positive, negative, and cognitive symptoms (N=15, 3 weeks; N=14, 6 weeks; N=40, 8 weeks; N=20, 2 weeks) (Feifel et al., 2010; Gibson et al., 2014; Modabbernia et al., 2013; Pedersen et al., 2011), respectively. However, more recent, larger clinical trials do not show robust benefits for positive or negative symptoms, either with OT alone (N=58, 6 weeks) (Buchanan et al., 2015; Weiser et al., 2015), or with social skills (N=48, 3 weeks) (Weiser et al., 2015) or social cognitive training (N=52, 6 weeks) (Cacciotti-Saija et al., 2015). We completed a pilot 3-week randomized, double-blind clinical trial (Lee et al., 2013) of OT vs. placebo (PBO). Negative symptoms improved only in inpatients who received OT.

It is important to understand the relationship between peripheral OT levels, symptoms and treatment response. Evidence remains equivocal regarding whether there are differences in peripheral levels of OT in individuals with SZ compared to controls, with some studies reporting higher levels (Strauss et al., 2015a; Strauss et al., 2015b; Strauss et al., 2015c), lower levels (Goldman et al., 2008; Jobst et al., 2014) or no difference (Rubin et al., 2014; Rubin et al., 2013; Rubin et al., 2010). There are mixed results also reported for central levels in individuals with SZ (Beckmann et al., 1985; Glover et al., 1994; Linkowski et al., 1984). There are associations between plasma OT levels and symptoms as well as social cognitive measures. OT levels either in plasma or CSF are inversely correlated with negative symptoms in men with SZ (Jobst et al., 2014; Keri et al., 2009; Sasayama et al., 2012). Lower plasma OT levels are also associated with more asociality and poorer accuracy for olfactory identification in individuals with SZ (Rubin et al., 2010; Strauss et al., 2015b). Lower peripheral levels of OT are associated with more severe positive symptoms, general psychopathology and poorer perception of emotion in women, but not men, with SZ (Rubin et al., 2011; Rubin et al., 2010; Strauss et al., 2015c).

There are no studies that examine the effects of *repeated* OT dosing versus PBO on 1) peripheral OT levels and 2) the relationship between changes in peripheral OT levels and changes in clinical symptoms. At baseline, we hypothesized that there would be a negative correlation between peripheral levels of OT and positive and negative symptoms of SZ. After repeated OT dosing compared to PBO, peripheral OT levels would increase with the increase in peripheral OT levels after 3 weeks significantly correlated with the improvement in positive and negative symptoms of SZ.

2. Materials and Methods

We conducted a double-blind randomized clinical trial of intranasal OT vs. PBO in participants (N=28) with SZ or schizoaffective disorder. Full information on study population, methods and results of this trial are presented elsewhere (Lee et al., 2013; Wehring et al., 2012). All participants underwent a two-week lead in period prior to randomization in the study. The study was conducted in the inpatient or outpatient setting with inpatients remaining hospitalized for the duration of the two week lead in and for three weeks post randomization to OT or PBO.

Intranasal OT (Syntocinon, Novartis) was supplied by PharmaWorld (Zurich, Switzerland). Intranasal PBO was prepared by Laboswiss (Davos, Switzerland) and contained all components of the Syntocinon except OT. Each participant was instructed to administer 20 IU of OT or PBO intranasally twice daily. Each 20 IU dose of OT consisted of five puffs, each containing 4 IU of OT. Intranasal OT was approved by the Food and Drug Administration (FDA) for use as an Investigational New Drug (IND).

Positive and negative symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS) (18 items, each scored 1–7) (Overall and Gorham, 1962) and the modified Scale for the Assessment of Negative Symptoms (SANS) (Buchanan et al., 2007), respectively. The BPRS 4-item positive symptom score measured positive and the SANS total score measured negative symptoms. Other BPRS factors were used to measure anxiety/depression, hostility and activation. The average of the SANS avolition and anhedonia/asociality global items was used to measure motivation and ability to experience pleasure that has been found to be separable from diminished emotional expressivity (restricted affect and alogia) (Blanchard and Cohen, 2006). Symptom measures were administered at baseline, before the first dose of OT/PBO and at endpoint, after the last dose of OT/PBO. All raters were blind to treatment assignment.

Plasma OT levels were drawn at in am before first and last dose of study medication. Correlations between baseline OT plasma levels and positive and negative symptom scores as well as the correlation between the change in OT levels and symptoms from baseline to 3 weeks were examined. OT levels were analyzed by Radioimmunoassay (RIA) following acetone-ether extraction. The minimum detectable concentration of OT in plasma was 0.25 pg/mL. The OT antiserum (Pitt-Ab) was specific for OT and displayed <1% cross-reactivity with vasopressin, a similar nonapeptide.

Data Analysis

Age was included as a covariate in all the modeling since there was a significant difference in average age between the treatment groups (Lee et al., 2013). Treatment group differences in plasma OT levels at endpoint were determined using the analysis of covariance (ANCOVA) model: end point score = baseline score + treatment group + age. Additional analyses, examining a treatment group (OT vs. PBO) x treatment setting (inpatient vs outpatient) interaction for treatment outcome measures, were conducted with the ANCOVA model: end point score = baseline score + treatment group + inpatient/outpatient status + treatment x inpatient/outpatient status + age. Spearman correlation coefficients were used to

assess baseline correlations between OT levels and psychiatric symptoms, as well as correlations between change scores for plasma OT levels and change scores for psychiatric symptoms. Differences in magnitude of Spearman correlations between OT and PBO groups were tested following Fisher's Z transformation. As this report contains exploratory analyses of secondary outcomes, no adjustment was made for multiple testing.

3. Results

Group characteristics are reported elsewhere (Lee et al., 2013). Participants were randomized to either adjunctive intranasal OT (N=13) or PBO (N=15). There were no significant differences in demographic variables except age which was higher in the OT group (44.7 ± 11.7 vs. 35.1 ± 8.2 years). At baseline, there were no significant treatment group differences in symptom measures (Lee et al., 2013), OT levels, or significant correlations between baseline OT levels and symptom measures. At baseline, the mean (s.d.) peripheral level of OT was 1.29 (0.48) pg/mL for the OT group and 0.93(0.36) pg/mL for the PBO ($t=3.65$, $df=1$ $p=0.056$). After 3 weeks, there was neither a significant treatment group difference in the change in plasma OT level ($F=0.71$, $df=1,22$, $p=0.41$) nor a significant interaction with treatment setting ($F=0.00$, $df=1,22$, $p=0.98$). There was no significant treatment group difference in the magnitude of the correlation between change in OT level and change in BPRS total score (Table 2, Figure 1a) or change in BPRS negative symptom score (Table 2, Figure 1b).

4. Discussion

Twice daily administration of intranasal OT (20 IU) over 3 weeks did not significantly increase endogenous plasma OT levels. There were also no significant associations between baseline peripheral OT levels and clinical symptoms. The correlation between change in peripheral OT levels and change in symptom levels was not different across treatment groups. This negative results of this study were possibly due to lack of power to detect treatment effects of the magnitude observed (effect size=0.33). Low power might also account for some inconsistencies across studies in the relationship between OT levels and symptoms. In addition, the limited sensitivity and specificity of OT measurement by radioimmunoassay (RIA) and enzyme immunoassay (EIA), respectively (Aasebo and Slordal, 1990), might contribute to these inconsistencies. Adherence to dosing with the nasal spray in outpatient trials might be another limitation. Only inpatients, subjects were observed administering OT or PBO via nasal spray. There was no procedure to quantify the amount of study drug administered.

More work is needed to characterize the relationship between OT blood levels and symptom measures as well as to understand the relationship between peripheral and central OT levels. Gender differences have been found in the relationship between blood OT levels and symptoms of schizophrenia in women, not men: lower peripheral levels of OT were associated cross-sectionally with more severe positive symptoms and general psychopathology and worse emotion perception (Rubin et al., 2011; Rubin et al., 2010; Strauss et al., 2015c). In clinical trials to date, OT is given as an adjunct to standard antipsychotic therapy. The latter suppresses dopaminergic as well as serotonergic signaling

and both of these neurotransmitters interact with OT to impact motivated behaviors (Skuse and Gallagher, 2009). It is unknown how antipsychotic medications affect the endogenous OT system and interact with exogenously delivered OT to impact psychotic and cognitive symptoms. Trials where OT is given as the sole therapy (after medication washout) are needed to determine the effect of OT directly on psychotic and cognitive symptoms in SZ.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Aasebo U, Slordal L. Transient reduction in serum cortisol levels after dexamethasone antiemetic therapy in cancer patients undergoing chemotherapy. *Acta Oncol.* 1990; 29(3):314–316. [PubMed: 2163661]
- Beckmann H, Lang RE, Gattaz WF. Vasopressin--oxytocin in cerebrospinal fluid of schizophrenic patients and normal controls. *Psychoneuroendocrinology.* 1985; 10(2):187–191. [PubMed: 4034849]
- Blanchard JJ, Cohen AS. The structure of negative symptoms within schizophrenia: implications for assessment. *Schizophrenia bulletin.* 2006; 32(2):238–245. [PubMed: 16254064]
- Buchanan, R.; Kelly, DL.; Strauss, GP.; Gold, JM.; McMahon, RP.; Wehring, HJ.; Weiner, E.; Osing, J.; Sullivan, K.; Feldman, S.; Adams, H.; Carpenter, WT. Oxytocin and Galantamine for the Treatment of Negative Symptoms and Cognitive Impairments in Schizophrenia. *International Congress on Schizophrenia Research; Colorado Springs, Colorado.* 2015.
- Buchanan RW, Javitt DC, Marder SR, Schooler NR, Gold JM, McMahon RP, Heresco-Levy U, Carpenter WT. The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST): the efficacy of glutamatergic agents for negative symptoms and cognitive impairments. *The American journal of psychiatry.* 2007; 164(10):1593–1602. [PubMed: 17898352]
- Cacciotti-Saija C, Langdon R, Ward PB, Hickie IB, Scott EM, Naismith SL, Moore L, Alvares GA, Redoblado Hodge MA, Guastella AJ. A double-blind randomized controlled trial of oxytocin nasal spray and social cognition training for young people with early psychosis. *Schizophr Bull.* 2015; 41(2):483–493. [PubMed: 24962607]
- Feifel D, Macdonald K, Nguyen A, Cobb P, Warlan H, Galangue B, Minassian A, Becker O, Cooper J, Perry W, Lefebvre M, Gonzales J, Hadley A. Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients. *Biol Psychiatry.* 2010; 68(7):678–680. [PubMed: 20615494]
- Gibson CM, Penn DL, Smedley KL, Leserman J, Elliott T, Pedersen CA. A pilot six-week randomized controlled trial of oxytocin on social cognition and social skills in schizophrenia. *Schizophr Res.* 2014; 156(2–3):261–265. [PubMed: 24799299]
- Glovinsky D, Kalogeras KT, Kirch DG, Suddath R, Wyatt RJ. Cerebrospinal fluid oxytocin concentration in schizophrenic patients does not differ from control subjects and is not changed by neuroleptic medication. *Schizophrenia research.* 1994; 11(3):273–276. [PubMed: 7910756]

- Goldman M, Marlow-O'Connor M, Torres I, Carter CS. Diminished plasma oxytocin in schizophrenic patients with neuroendocrine dysfunction and emotional deficits. *Schizophr Res*. 2008; 98(1–3): 247–255. [PubMed: 17961988]
- Jobst A, Dehning S, Ruf S, Notz T, Buchheim A, Henning-Fast K, Meissner D, Meyer S, Bondy B, Muller N, Zill P. Oxytocin and vasopressin levels are decreased in the plasma of male schizophrenia patients. *Acta Neuropsychiatr*. 2014; 26(6):347–355. [PubMed: 25288094]
- Keri S, Kiss I, Kelemen O. Sharing secrets: oxytocin and trust in schizophrenia. *Soc Neurosci*. 2009; 4(4):287–293. [PubMed: 18671168]
- Lee MR, Wehring HJ, McMahon RP, Linthicum J, Cascella N, Liu F, Bellack A, Buchanan RW, Strauss GP, Contoreggi C, Kelly DL. Effects of adjunctive intranasal oxytocin on olfactory identification and clinical symptoms in schizophrenia: results from a randomized double blind placebo controlled pilot study. *Schizophr Res*. 2013; 145(1–3):110–115. [PubMed: 23415472]
- Linkowski P, Geenen V, Kerkhofs M, Mendlewicz J, Legros JJ. Cerebrospinal fluid neuropeptides in affective illness and in schizophrenia. *European archives of psychiatry and neurological sciences*. 1984; 234(3):162–165. [PubMed: 6489403]
- Modabbernia A, Rezaei F, Salehi B, Jafarinia M, Ashrafi M, Tabrizi M, Hosseini SM, Tajdini M, Ghaleiha A, Akhondzadeh S. Intranasal oxytocin as an adjunct to risperidone in patients with schizophrenia : an 8-week, randomized, double-blind, placebo-controlled study. *CNS drugs*. 2013; 27(1):57–65. [PubMed: 23233269]
- Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep*. 1962; 10(79):812.
- Pedersen CA, Gibson CM, Rau SW, Salimi K, Smedley KL, Casey RL, Leserman J, Jarskog LF, Penn DL. Intranasal oxytocin reduces psychotic symptoms and improves Theory of Mind and social perception in schizophrenia. *Schizophr Res*. 2011; 132(1):50–53. [PubMed: 21840177]
- Rubin LH, Carter CS, Bishop JR, Pournajafi-Nazarloo H, Drogos LL, Hill SK, Ruocco AC, Keedy SK, Reilly JL, Keshavan MS, Pearlson GD, Tamminga CA, Gershon ES, Sweeney JA. Reduced levels of vasopressin and reduced behavioral modulation of oxytocin in psychotic disorders. *Schizophr Bull*. 2014; 40(6):1374–1384. [PubMed: 24619535]
- Rubin LH, Carter CS, Bishop JR, Pournajafi-Nazarloo H, Harris MS, Hill SK, Reilly JL, Sweeney JA. Peripheral vasopressin but not oxytocin relates to severity of acute psychosis in women with acutely-ill untreated first-episode psychosis. *Schizophr Res*. 2013; 146(1–3):138–143. [PubMed: 23465965]
- Rubin LH, Carter CS, Drogos L, Jamadar R, Pournajafi-Nazarloo H, Sweeney JA, Maki PM. Sex-specific associations between peripheral oxytocin and emotion perception in schizophrenia. *Schizophr Res*. 2011; 130(1–3):266–270. [PubMed: 21684122]
- Rubin LH, Carter CS, Drogos L, Pournajafi-Nazarloo H, Sweeney JA, Maki PM. Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. *Schizophr Res*. 2010; 124(1–3):13–21. [PubMed: 20947304]
- Sasayama D, Hattori K, Teraishi T, Hori H, Ota M, Yoshida S, Arima K, Higuchi T, Amano N, Kunugi H. Negative correlation between cerebrospinal fluid oxytocin levels and negative symptoms of male patients with schizophrenia. *Schizophr Res*. 2012; 139(1–3):201–206. [PubMed: 22742979]
- Skuse DH, Gallagher L. Dopaminergic-neuropeptide interactions in the social brain. *Trends in cognitive sciences*. 2009; 13(1):27–35. [PubMed: 19084465]
- Strauss GP, Keller WR, Koenig JI, Gold JM, Frost KH, Buchanan RW. Plasma oxytocin levels predict social cue recognition in individuals with schizophrenia. *Schizophrenia research*. 2015a; 162(1–3): 47–51. [PubMed: 25673435]
- Strauss GP, Keller WR, Koenig JI, Gold JM, Ossenfort KL, Buchanan RW. Plasma oxytocin levels predict olfactory identification and negative symptoms in individuals with schizophrenia. *Schizophr Res*. 2015b; 162(1–3):57–61. [PubMed: 25583247]
- Strauss GP, Keller WR, Koenig JI, Sullivan SK, Gold JM, Buchanan RW. Endogenous oxytocin levels are associated with the perception of emotion in dynamic body expressions in schizophrenia. *Schizophr Res*. 2015c; 162(1–3):52–56. [PubMed: 25620121]
- Wehring H, Lee M, McMahon R, Bellack A, Linthicum J, Feldman S, Vyas G, Richardson C, Buchanan R, Contoreggi C, Kearns A, Kelly D. Intranasal Oxytocin Effects On Social Anxiety

And Depression in Schizophrenia: Results From A Double Blind Placebo Controlled Trial. Schizophrenia research. 2012; 136(Supplement 1):S360.

Weiser, M.; Saporta, L.; Levi, L.; Feldman, R. Oxytocin for Schizophrenia: A Randomized Controlled Trial. International Congress on Schizophrenia Research; Colorado Springs, Colorado. 2015.

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Figure 1a
Correlation between Oxytocin Level and BPRS Total Score

Figure 1b
Correlation between Oxytocin Level and BPRS Negative Symptoms

Figure 1.
Figure 1a. Association between the change score in peripheral oxytocin (OT) levels (baseline – 3 weeks) and the change score in the BPRS total score (baseline – 3 weeks). Improvement is noted by negative values for change in BPRS total score. Oxytocin level units are pg/mL

Figure 1b. Association between the change score in peripheral oxytocin (OT) levels (baseline – 3 weeks) and the change score in the BPRS negative symptom score (baseline – 3 weeks).

Improvement is noted by negative values for change in BPRS negative symptom score.

Oxytocin level units are pg/mL

Table 1

Peripheral oxytocin (OT) levels (pg/mL) by group and treatment setting

	Peripheral OT levels		Percent Change from Baseline
	Baseline M (SD)	Endpoint M (SD)	
OT Group	1.29 (0.48)	1.46 (0.69)	13.2
PBO Group	0.93 (0.36)	1.11 (0.41)	19.4
Inpatient OT Group (N=6)	1.06 (0.26)	1.30 (0.63)	22.6
Inpatient PBO Group(N=6)	0.79 (0.28)	1.00 (0.16)	26.6
Outpatient OT Group (N=7)	1.49 (0.55)	1.59 (0.76)	6.7
Outpatient PBO Group (N=9)	1.02 (0.39)	1.18 (0.51)	15.7

Table 2

Associations between the change score in peripheral oxytocin (OT) levels (pg/mL) (baseline – 3 weeks) and the change score in clinical symptoms (baseline – 3 weeks).

	Group		Z, p
	OT (n=13) r	PBO (n=15) R	
BPRS			
Total score	-0.57*	-0.18	-1.09, 0.27
Negative symptom score	-0.57*	0.02	-1.55, 0.12
Psychotic symptom score	-0.09	-0.27	0.44, 0.66
Anxiety/depressive symptom score	-0.07	-0.03	-0.09, 0.93
Hostility score	-0.32	0.20	-1.25, 0.21
Activation score	-0.31	-0.24	-0.18, 0.86
SANS			
Total score	-0.24	-0.46	0.59, 0.55
Anhedonia/asociality global item	0.26	-0.31	-1.37, 0.17

Note.

*
p<0.05.

BPRS= Brief Psychiatric Rating Scale; SANS= Scale for the Assessment of Negative Symptoms; Z=Fisher's r-to-z transformation 2-tailed test.
p=p-value for test of treatment difference in the magnitude of correlations.