Intranasal oxytocin reduces psychotic symptoms and improves Theory of Mind and social perception in schizophrenia

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ABSTRACT

Oxytocin has numerous prosocial and antipsychotic-like effects in animals. Prosocial effects of acute intranasal oxytocin administration have also been reported in human subjects. We conducted a randomized, placebo-controlled trial testing the effects of twice daily intranasal oxytocin treatment for 14 days on psychotic symptoms and social cognition in patients with schizophrenia. PANSS scores declined significantly and several social cognition measures improved significantly or nearly significantly in oxytocin (N = 11) but not placebo (N = 9) recipients. Our results suggest that, in addition to reducing classic psychotic symptoms, oxytocin may diminish certain social cognition deficits that are not improved by current antipsychotic medications.

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1. Introduction

Social impairment is a primary cause of disability in schizophrenia, responds poorly to current antipsychotic medications and is related to deficits in social cognitive abilities, which include Theory of Mind, emotion recognition and attributional style (Fett et al., 2011; Green et al., 2005; Penn et al., 2009).

Oxytocin (OT) has many pro-social effects in animals (Carter et al., 1998; Gimpl and Fahrenholz, 2001; Lee et al., 2009; Pedersen et al., 1992) and antipsychotic-like efficacy in preclinical tests (Caldwell et al., 2009; Feifel and Reza, 1999; Lee et al., 2005; 2007). Acute intranasal OT administration in human subjects may elevate OT concentrations in the brain (Born et al., 2002), increase positive social behavior (e.g., interpersonal trust, eye gaze) and improve social cognition (MacDonald and MacDonald, 2010). In patients with schizophrenia, plasma OT concentrations are lower than normal subjects and correlate negatively with psychotic symptoms (Keri et al., 2009; Rubin et al., 2010). Daily intranasal OT treatment for 3 weeks was recently reported to decrease psychotic symptoms in schizophrenia (Feifel et al., 2010).

Based on this body of research, we hypothesized that sustained daily intranasal administration of OT would improve social cognition as well as reduce psychotic symptoms in schizophrenia.

2. Materials and methods

2.1. Subjects

Twenty-three subjects were enrolled; 2 dropped out before randomization to treatment and 1 dropped out early because he developed an upper respiratory infection; the remaining 20 completed the protocol and constitute our study sample. Inclusion criteria were: 18–55 years of age, DSM-IV diagnosis of paranoid or undifferentiated schizophrenia ≥ 1 year, PANSS total score ≥ 60, PANSS suspiciousness/persecutory item score ≥ 4 or 3 on this item and ≥ 3 on at least one other social behavior-relevant PANSS item (hostility, passive/apathetic social withdrawal, uncooperativeness, active social withdrawal), treatment with one or more standard antipsychotic medications, stability of medication doses and symptoms ≥ 1 month. See Table S1 (Supplement 1) for exclusion criteria.

The study was approved by the University of North Carolina Biomedical Institutional Review Board and conducted in accordance with The Code of Ethics of the World Medical Association. Written informed consent was obtained from all subjects.

2.2. Procedures

This was a randomized, double blind, placebo-controlled 2-week treatment trial. Screening of subjects included a review of psychiatric and medical history, physical examination, an ECG, and blood and urine collection for standard laboratory tests. Within 1 week after

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screening, baseline social cognition measures were obtained followed by psychiatric ratings. Daily intranasal treatments were initiated after baseline assessments. Social cognition measures and psychiatric ratings were repeated beginning 50 min after the AM dose of study medication on treatment day 14. The social cognition instruments were the Brüne Theory of Mind Picture Stories Task (Brüne, 2003) and the Trustworthiness Task (Adolphs et al., 1998). Psychiatric measures included the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987) and the Paranoia Scale (Fenigstein and Vanable, 1992). The first 10 subjects were studied as inpatients on a clinical research unit (5 received OT, 5 placebo) and the last 10 subjects were studied in an outpatient research clinic (6 OT, 4 placebo). Blood and urine laboratory tests, ECGs and body weights were obtained at screening and treatment day 14 in all subjects and also on treatment days 3 and 7 in inpatients.

2.3. Study drugs

Subjects remained on their pre-study medication regimen and doses throughout the treatment trial. They self-administered intranasal study drug twice daily; before breakfast and before dinner. Each dose consisted of six 0.1 ml insufflations (alternating between the left and right nostril) of OT spray containing approximately 24 international units of OT [Syntocinon Spray, Novartis] or placebo. Twenty four IU is by far the most commonly used dose in studies that found significant effects of acute intranasal OT treatment (MacDonald and MacDonald, 2010). Outpatient compliance with test treatments was monitored by weighing spray vials before they were dispensed and after the morning dose on treatment day 14.

2.4. Statistical analyses

All dependent variables were examined for normality and skewness prior to analyses. We compared OT and placebo group means using an unpaired t test for the following baseline variables: demographic, psychiatric history and diagnosis, inpatient versus outpatient status, social cognition and psychiatric measures. We performed a paired t test within each treatment group examining changes from baseline to two weeks on the following variables: biological (laboratory test values, vital signs), social cognition measures (Brüne Task, Trustworthiness Task), and psychiatric measures (PANSS total and subscales, Paranoia Scale). To compare the treatment groups over time on social cognition and psychiatric variables, we used analysis of covariance controlling for the baseline measure of the dependent variable.

3. Results

The sample consisted of 17 men and 3 women: 10 Caucasian and 10 African-American. There were no significant demographic or psychiatric history differences between the treatment groups (Table 1). These data and psychotropic medications are summarized for each subject in Table S2 in Supplement 1. Neither treatment group had clinically or statistically significant changes over the 14-day treatment period in laboratory safety measures (CBC, electrolytes, glucose, BUN, creatinine, liver functions, urinalysis), ECGs or vital signs.

Table 2 summarizes the results. There were no differences between treatment groups at baseline on any of the outcome variables. The OT group had significant improvements from baseline to treatment day 14 in accurate identification of second order false belief in the Brüne Task as well as significant reductions in PANSS total, positive subscale, general subscale, suspiciousness/persecutory item, anxiety item and Paranoia Scale scores. In addition, OT recipients showed trends toward significant improvement in accurate recognition of deception in the Brüne Task, rating untrustworthy faces (faces rated by a normative sample as untrustworthy) as less untrustworthy

Table 1
Descriptive data for oxytocin (OT) and placebo participants.

Variable	OT (n = 11)		Placebo (n = 9)	
	N	%	N	%
Male	9	82	8	89
Ethnicity				
African-American	5	45	5	56
Caucasian	6	55	4	44
Diagnosis				
PS	10	91	7	78
US	1	9	2	22
Inpatient	5	45	5	56
	Mean	SD	Mean	SD
Age	39.00	11.18	35.78	9.52
Years of education	12.27	1.01	12.56	1.51
Years of illness	16.00	11.08	12.89	9.43
Hospitalizations	7.82	7.90	7.11	7.93

PS = paranoid schizophrenia; US = undifferentiated schizophrenia; Years of illness = number of years since diagnosis of schizophrenia; Hospitalizations = number of psychiatric hospitalizations.

and reductions in PANSS negative subscale scores. The OT group had no changes that approached statistical significance in other Brüne Task measures that have been reported to differ between patients with schizophrenia and healthy controls (second order belief, third order false belief, recognition of cheating; Brüne, 2005). In the placebo group, the only significant change during the treatment period was a decline in PANSS suspiciousness item scores.

ANCOVAs controlling for baseline revealed that the OT group (Least squared [LS] mean = 70.56; SE = 2.07), compared to the placebo group (LS mean = 77.21; SE = 2.29), had a significantly greater decline in PANSS total scores (F = 4.60, p = .047). There was also a trend toward a significantly greater decline in PANSS general subscale scores (F = 3.78, p = .069) for the OT group (LS mean = 34.34; SE = 1.35) compared to placebo (LS mean = 38.26; SE = 1.49). There were no group differences in change over the treatment period for other PANSS or social cognition variables.

4. Discussion

Our results are the first indicating that OT treatment may improve social cognition in schizophrenia. Furthermore, our findings are consistent with the recent report from Feifel et al. (2010) that a relatively brief period of daily intranasal OT treatment reduces psychotic symptoms in medicated patients with schizophrenia.

The improvements in aspects of social cognition in OT recipients are particularly exciting. Social cognition deficits in schizophrenia are among a number of important factors (e.g. negative symptoms) that have been linked to social dysfunction (Couture et al., 2006; Fett et al., 2011), a major cause of disability in schizophrenia and the aspect of the disorder that is least responsive to currently available antipsychotic medications (Penn et al., 2009). Therefore, improvements in social cognition associated with OT treatment could potentially be accompanied by improvements in social functioning.

This report has several limitations that require cautious interpretation of our results. Our sample size was small and the treatment trial duration brief. We present data from only two social cognition tests, the Brüne Theory of Mind Picture Stories Task and the Trustworthiness Task. We don't know yet whether our results generalize to other social cognition domains. Other instruments were administered to quantify emotion recognition, attributional style and social skill. However, the data from these measures were not available at the time of this submission. In addition, basic neurocognition was not assessed, thus we cannot confidently conclude that OT has a specific impact on social cognition (rather than cognition in general). Higher (non-significantly) baseline social cognition measures in placebo recipients confounded

Table 2
Outcome measures: means, standard deviations and ranges.

	Oxytocin ($n = 11$)				Placebo ($n = 9$)			
	Baseline		Day 14		Baseline		Day 14	
	M (SD)	Range	M (SD)	Range	M (SD)	Range	M (SD)	Range
Brüne 2nd false	1.91 (.83)	1–3	2.45 (.69)[c]	1–3	2.11 (.60)	1–3	2.33 (.87)	1–3
Brüne deception	2.27 (.79)	1–3	2.82 (.40)[a]	2–3	2.22 (.83)	1–3	2.44 (.73)	1–3
Brüne 2nd order	2.00 (.00)	2–2	2.00 (.00)	2–2	2.00 (.00)	2–2	2.00 (.00)	2–2
Brüne 3rd false	2.00 (1.10)	0–3	2.36 (1.03)	0–3	2.44 (.53)	2–3	2.44 (.88)	1–3
Brüne cheating	2.00 (.00)	2–2	1.82 (.41)	1–2	1.89 (.33)	1–2	2.00 (.00)	2–2
Trustworthiness	−15.82 (15.03)	−36–+20	−9.36 (12.33)[a]	−36–+11	−3.33 (12.19)	−18–+15	−6.44 (12.47)	−19–+17
PANSS total score	82.91 (13.59)	61–101	71.82 (11.29)[d]	51–86	78.89 (16.75)	58–110	75.67 (13.73)	57–106
PANSS positive	20.46 (5.80)	9–30	17.73 (5.44)[c]	9–26	21.67 (6.91)	13–30	20.44 (5.50)	13–27
PANSS negative	21.00 (4.12)	13–28	18.91 (3.81)[a]	13–28	19.11 (3.98)	13–26	18.00 (3.67)	12–24
PANSS general	40.64 (7.84)	28–49	35.18 (6.48)[c]	24–44	38.22 (10.41)	25–58	37.22 (10.08)	24–59
PANSS suspicious	4.45 (0.69)	3–5	3.73 (1.01)[c]	2–5	4.22 (.97)	3–6	3.78 (.83)[b]	3–5
PANSS anxiety	2.73 (1.19)	1–5	1.91 (1.58)[b]	1–5	3.44 (1.67)	1–6	2.89 (1.54)	1–6
Paranoia Scale	48.73 (21.53)	23–82	44.91 (21.48)[b]	22–82	42.56 (14.83)	20–63	39.44 (16.75)	20–66

Range = observed range of scores; Brüne = Brüne Theory of Mind Picture Stories Task; Brüne 2nd false = 2nd order false belief identification score on Brüne Task; Brüne deception = deception identification score; Brüne 2nd order = 2nd order belief identification score; Brüne 3rd false = 3rd order false belief identification score; Brüne cheating = cheating identification score; Trustworthiness = Trustworthiness Task score on untrustworthy faces (scored below the mean by normative group); PANSS = Positive and Negative Symptom Scale; PANSS positive = positive symptom subscale score on PANSS; PANSS negative = negative symptom subscale score on PANSS; PANSS general = general symptom subscale score on PANSS; PANSS suspicious = PANSS suspiciousness/persecutory item score; PANSS anxiety = PANSS anxiety item score. Superscripts indicate significant within-group differences using paired comparisons t-tests between baseline and day 14.
a = p ≤ .08, b = p < .05, c = p < .01, d = p < .001; day 14 mean compared to baseline mean.

group comparisons. Longer treatment trials in larger subject samples employing more comprehensive batteries of instruments will be necessary to adequately test whether OT treatment improves all social cognition domains, further reduces psychotic symptoms and enhances social/community functioning.

If longer trials are confirmatory, other questions about OT treatment will require investigation. Is OT solely an augmentor of antipsychotic medications or also an efficacious monotherapy? Would OT treatment increase the effectiveness of psychosocial interventions targeting social cognition (Horan et al., 2008; Roberts et al., 2010)? Can OT treatment stave off the social and functional deterioration occurring early in the course of schizophrenia (first episode) or progression from prodromal symptoms to schizophrenia? Is OT treatment effective in other psychotic disorders or for psychotic symptoms in mood disorders? Furthermore, confirmation that OT treatment is efficacious would establish CNS OT as an important new front in preclinical and clinical investigation of schizophrenia pathophysiology.

Contributors

Authors CAP, DLP, SWR, KS and LFJ collaborated on designing the study; CAP, DLP, CMG, KLS and RLC wrote the protocol and obtained IRB approval. CMG, KLS and RLC coordinated execution of the project. JLS analyzed the data. CAP wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

CAP has submitted U.S. Provisional Patent Application 61/346,347 but otherwise has no potential conflicts of interest. LFJ has received research grant support from GSK and Novartis. All other authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.schres.2011.07.027.

References

Adolphs, R., Tranel, D., Damasio, A.R., 1998. The human amygdala in social judgment. Nature 393, 470–474.

Born, J., Lange, T., Kern, W., McGregor, G.P., Bickel, U., Fehm, H.L., 2002. Sniffing neuropeptides: a transnasal approach to the human brain. Nat. Neurosci. 5, 514–516.

Brüne, M., 2003. Social cognition and behaviour in schizophrenia. In: Brüne, M., Ribbert, H., Schiefenhövel, W. (Eds.), The Social Brain-Evolution and Pathology. John Wiley & Sons, Chichester, pp. 277–313.

Brüne, M., 2005. Emotion recognition, "theory of mind", and social behavior in schizophrenia. Psychiatry Res. 133, 135–147.

Caldwell, H.K., Stephens, S.L., Young, W.S.I.I.I., 2009. Oxytocin as a natural antipsychotic: a study using oxytocin knockout mice. Mol. Psychiatry 14, 190–196.

Carter, C.S., Lederhendler, I., Kirkpatrick, B., 1998. The Integrative Neurobiology of Affiliation. MIT Press, Cambridge, MA.

Couture, S.M., Penn, D.L., Roberts, D.L., 2006. The functional significance of social cognition in schizophrenia: a review. Schizophr. Bull. 32 (1), S44–SS63.

Feifel, D., Reza, T., 1999. Oxytocin modulates psychotomimetic-induced deficits in sensorimotor gating. Psychopharmacology (Berl.) 141, 93–98.

Feifel, D., MacDonald, K., Nguyen, A., Cobb, P., Warlan, H., Galangue, B., Minassian, A., Becker, O., Cooper, J., Perry, W., Lefebvre, M., Gonzalez, J., Hadley, A., 2010. Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients. Biol. Psychiatry 68, 678–680.

Fenigstein, A., Vanable, P., 1992. Persecutory ideation and self consciousness. J. Pers. Soc. Psych. 62, 129–138.

Fett, A.J., Viechtbauer, W., Dominguez, M., Penn, D.L., van Os, J., Krabbendam, L., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci. Biobehav. Rev. 35, 573–588.

Gimpl, G., Fahrenholz, F., 2001. The oxytocin receptor system: structure, function, and regulation. Physiol. Rev. 81, 629–683.

Green, M.F., Olivier, B., Crawley, J.N., Penn, D.L., Silverstein, S., 2005. Social cognition in schizophrenia: recommendations from the MATRICS New Approaches Conference. Schizophr. Bull. 31, 882–887.

Horan, W.P., Kern, R.S., Green, M.F., Penn, D.L., 2008. Social cognition training for individuals with schizophrenia: emerging evidence. Am. J. Psychiatric Rehab. 11 (3), 205–252.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Keri, S., Kiss, I., Kelemen, O., 2009. Sharing secrets: oxytocin and trust in schizophrenia. Soc. Neurosci. 4, 287–293.

Lee, P.R., Brady, D.L., Shapiro, R.A., Dorsa, D.M., Koenig, J.I., 2005. Social interaction deficits caused by chronic phencyclidine administration are reversed by oxytocin. Neuropsychopharmacology 30, 1883–1894.

Lee, P.R., Brady, D.L., Shapiro, R.A., Dorsa, D.M., Koenig, J.I., 2007. Prenatal stress generates deficits in rat social behavior: reversal by oxytocin. Brain Res. 1156, 152–167.

Lee, H.-J., Macbeth, A.H., Pagani, J.H., Young, W.S.I.I.I., 2009. Oxytocin: the great facilitator of life. Prog. Neurobiol. 88, 127–151.

MacDonald, K., MacDonald, T.M., 2010. The peptide that binds: a systematic review of oxytocin and its prosocial effects in humans. Harv. Rev. Psychiatry 18, 1–21.

Pedersen, C.A., Caldwell, J.D., Jirikowski, G.F., Insel, T.R., 1992. Oxytocin in maternal, sexual and social behaviors. Ann. N. Y. Acad. Sci. 652.

Penn, D.L., Keefe, R.S., Davis, S.M., Meyer, P.S., Perkins, D.O., Losardo, D., Lieberman, J.A., 2009. The effects of antipsychotic medications on emotion perception in patients with chronic schizophrenia in the CATIE trial. Schizophr. Res. 115 (1), 17–23.

Roberts, D.L., Penn, D.L., Labate, D., Margolis, S.A., Sterne, A., 2010. Transportability and feasibility of Social Cognition And Interaction Training (SCIT) in community settings. Behav. Cogn. Psychother. 38, 35–47.

Rubin, L.H., Carter, C.S., Drogos, L., Pournajafi-Nazarloo, H., Sweeney, J.A., Maki, P.M., 2010. Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. Schizophr. Res. 124, 13–21.