

Oxytocin Increases Retention of Social Cognition in Autism

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Background: Oxytocin dysfunction might contribute to the development of social deficits in autism, a core symptom domain and potential target for intervention. This study explored the effect of intravenous oxytocin administration on the retention of social information in autism.

Methods: Oxytocin and placebo challenges were administered to 15 adult subjects diagnosed with autism or Asperger's disorder, and comprehension of affective speech (happy, indifferent, angry, and sad) in neutral content sentences was tested.

Results: All subjects showed improvements in affective speech comprehension from pre- to post-infusion; however, whereas those who received placebo first tended to revert to baseline after a delay, those who received oxytocin first retained the ability to accurately assign emotional significance to speech intonation on the speech comprehension task.

Conclusions: These results are consistent with studies linking oxytocin to social recognition in rodents as well as studies linking oxytocin to prosocial behavior in humans and suggest that oxytocin might facilitate social information processing in those with autism. These findings also provide preliminary support for the use of oxytocin in the treatment of autism.

Key Words: Autism, oxytocin, neuropeptide, social cognition, affective speech

Autism is a developmental disorder characterized by abnormalities in speech and communication, impaired social functioning, and repetitive behaviors and restricted interests (American Psychiatric Association 2000). A number of researchers have suggested that the neuropeptide oxytocin might be implicated in the etiology of autism (Bartz and Hollander, in press; Hollander et al 2003; Insel 1997; Insel et al 1999; Lim et al 2005; McCarthy and Altemus 1997; Modahl et al 1992; Panksepp 1992; Waterhouse et al 1996). Oxytocin is a nine-amino-acid peptide (nonapeptide) that is synthesized in the paraventricular and supraoptic nucleus of the hypothalamus and released into the bloodstream by way of axon terminals in the posterior pituitary. In addition to its release in systemic circulation, oxytocin is widely distributed throughout the central nervous system, and there are prominent oxytocin receptor binding sites, especially throughout the limbic system (Insel and Young 2000). Oxytocin is well-known for its effects on facilitating uterine contractions during parturition and milk let-down; however, oxytocin and the structurally similar peptide, vasopressin (two amino acids differentiate them), have also been found to be critically involved in affiliative behaviors, including sexual behavior, mother-infant and adult-adult pair-bond formation, separation distress, and other aspects of social attachment. Finally, although less central to the current investigation, oxytocin has been found to be involved in regulating feeding, grooming, and stress response (McCarthy and Altemus 1997).

Given that deficits in social interaction and affiliation are a core feature of autism and that oxytocin is involved in the regulation of affiliative behaviors, it is believed that oxytocin might play a role in autism. Waterhouse et al (1996) theorize that

aberrant functioning of the oxytocin and vasopressin neuropeptide systems contribute to the "asociality" that characterize those with autism, that is, the decreased interest in others and decreased desire to form social bonds. Preliminary findings by this group support the notion of dysregulated oxytocin in autism. Modahl et al (1998) found significantly lower levels of plasma oxytocin in 29 children diagnosed with autism compared with 30 age-matched healthy control children and also found that the autistic children in their study did not evidence the normal developmental increase in oxytocin blood levels that was characteristic of the healthy control children. These researchers also found a significant correlation between oxytocin levels and social impairment in a subgroup of their sample identified as severely affected (i.e., "aloof"). In a follow-up study, Green et al (2001) investigated whether these autistic children evidence alterations in oxytocin peptide forms and found higher levels of the precursor for oxytocin, termed OT-X, in the autistic children compared with controls, suggesting that autism might be related to differences in the way oxytocin is processed in the brain. Although these findings are based on peripheral rather than central oxytocin and await replication, they provide persuasive preliminary support for the involvement of oxytocin in autism.

Taking a different track, Hollander et al (2003) drew upon the findings from animal studies pointing to the role of oxytocin and vasopressin in excessive grooming and repetitive behaviors and investigated the influence of oxytocin infusion on repetitive behaviors in autism. In a double-blind cross-over design, autism spectrum disordered patients (i.e., those diagnosed with autism or Asperger's disorder) showed a significant reduction in repetitive behaviors—need to know, repeating, ordering, need to tell/ask, self-injury, and touching—after oxytocin infusion versus placebo infusion. Inspired by these findings, we sought to investigate the effects of oxytocin infusion on another core symptom domain of autism—social cognition.

Animal studies, mainly with rodents, suggest that oxytocin plays a role in social recognition and the processing of social cues. Popik et al (1992) investigated the effects of oxytocin on social recognition in rodents by assessing the duration of olfactory investigation of another rodent (a "conspecific") over repeated encounters and found that low (but not high) doses of oxytocin, administered centrally or peripherally, facilitated social recognition. Other researchers have found that centrally admin-

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istered oxytocin antagonists disrupt social memory in female rats (Engelmann et al 1998). More recently, Ferguson et al (2000) found that, compared with wild-type mice, male mice with a null mutation in the gene coding for oxytocin (“oxytocin knockout mice”) failed to recognize a conspecific even over repeated exposures; importantly, additional analyses revealed that this finding was not due to more general deficits in olfaction, learning, or memory. Other research by Choleris et al (2003) yielded similar results with female mice lacking the oxytocin gene. Moreover, in a follow-up study, Ferguson et al (2001) found that a single intracerebroventricular injection of oxytocin before the initial encounter with the conspecific enabled social memory acquisition (Ferguson et al 2001). Interestingly, the fact that social recognition was facilitated by injections occurring before but not those after the initial encounter with the conspecific suggests that oxytocin plays a role in social memory acquisition but not in social memory retrieval (Ferguson et al 2001).

To our knowledge, no studies have investigated the effects of oxytocin on social recognition per se in humans; however, two recent investigations suggest that oxytocin plays an important role in facilitating human social interactions. Kosfeld et al (2005) conducted a study in which intranasal oxytocin or placebo was administered to male university students playing “the trust game,” in which participants make decisions about transferring money to an anonymous player; trusting that the other player can lead to higher payoffs for both players because the money is tripled when transferred; but one runs the risk that the other player might violate one’s trust and not share his or her earnings. Results revealed that oxytocin significantly increased trust among participants compared with placebo. Moreover, the effects of oxytocin were not simply due to an increased willingness to engage in risky behavior; rather, they were due to participants’ willingness to accept social risks, suggesting that oxytocin is involved in prosocial approach behavior (Kosfeld et al 2005).

Another recent investigation by Kirsch et al (2005) also points to the role of oxytocin in mediating human social behavior. Healthy male participants were given intranasal oxytocin or placebo, and functional magnetic resonance imaging was used to investigate amygdala activity in response to fear-inducing stimuli of a social (angry and fearful faces) and non-social (threatening scenes) nature. Oxytocin reduced amygdala activation to both kinds of stimuli but, interestingly, had a more pronounced effect on the social stimuli. Moreover, results revealed that oxytocin reduced the functional connection between the amygdala and structures in the upper brain stem (i.e., the periaqueductal gray and reticular formation), which have been implicated in autonomic and behavioral fear responses. This study is consistent with previous studies documenting the anxiolytic effects of oxytocin and, as the authors’ suggest, point to the possibility that oxytocin might increase trust and prosocial behavior more generally by dampening amygdala responsiveness to the potential dangers inherent in social situations (i.e., by dampening social fear).

Thus, given the promising findings from animal studies suggesting that oxytocin plays an important, facilitating role in social recognition, the findings from human studies documenting the prosocial effects of oxytocin, and our findings showing that oxytocin reduced repetitive behaviors in autism, we sought to investigate whether increased levels of oxytocin would facilitate social information processing for individuals diagnosed with autism or autism spectrum disorders. We chose to focus on auditory processing of social stimuli—and specifically partici-

pants’ ability to assign affective significance to speech—because this deficit is present in most autistic people, and it has been hypothesized that its disruption could be central to the social and speech deficits in autism (Gervais et al 2004; Kuhl et al 2005).

Methods and Materials

Participants

In this randomized, placebo-controlled, double-blind cross-over investigation, 15 adults (14 men; mean age = 32.9 years, range = 19–56 years) diagnosed with autism ($n = 6$) or Asperger’s disorder ($n = 9$) received oxytocin and placebo challenges during visits separated by a minimum of 1 week (except for 1 subject in each group, for whom the delay was 3 days). Participants were medically healthy and medication-free for at least 2 weeks before and throughout the study. After receiving a complete description of the study, participants and/or their guardians signed written informed consent. The study was approved by the Mount Sinai School of Medicine Institutional Review Board and was conducted in accordance with the guidelines for conduct of ethical research involving human subjects as outlined by the National Institutes of Health.

All patients first underwent a diagnostic interview with the study psychiatrist, in which DSM-IV criteria were established with a diagnostic checklist for autism or Asperger’s disorder. In addition to the clinical screening interview, the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al 1994) was used to confirm diagnosis. The ADI-R is a semistructured psychiatric interview designed for the study of autism and related disorders; the interview is conducted with the patient’s parent or guardian and employs a diagnostic algorithm to differentiate autistic from non-autistic mentally handicapped individuals (Le Couteur et al 1989). In the present investigation, the ADI-R was administered by an ADI-trained and certified psychiatrist or clinical psychologist (interrater reliability was at least .80); informants were participants’ parents or guardians. Means and SDs for the social, communication, and repetitive behaviors category are presented in Table 1. It should be noted that we were unable to confirm autism/Asperger’s diagnosis with the ADI-R for 2 of the 15 patients in this study, because they did not have reliable informants. As a result, we ran all analyses with and without these patients; although the results did not change substantially when these patients were not included in the analyses and, in fact, were slightly stronger, we elected to report the analyses including these patients so that the findings are based on all available data.

Finally, the Peabody Picture Vocabulary Test-Revised (Dunn and Dunn 1981), which has been found to be strongly correlated with many measures of verbal IQ (Dunn and Dunn 1997, 1981), and the Raven’s Progressive Matrices (Raven 1958) were admin-

Table 1. Participant Characteristics

| | Mean | SD |
|------------------------------|--------|-------|
| ADI-R | | |
| Social | 21.23 | 7.43 |
| Communication (verbal) | 14.38 | 4.48 |
| Repetitive Behaviors | 7.08 | 3.99 |
| IQ | | |
| Raven’s Progressive Matrices | 111.91 | 17.51 |
| PPVT-R | 105.45 | 21.45 |

Raven’s Progressive Matrices (Raven 1958).

ADI-R, Autism Diagnostic Interview-Revised (Lord et al 1994); PPVT-R, Peabody Picture Vocabulary Test-Revised (Dunn and Dunn 1981).

istered to estimate verbal and non-verbal IQ. Overall, participants in the present investigation had average to above average verbal and non-verbal estimates of intelligence (see Table 1).

Oxytocin Administration

Each subject served as his or her own control and completed both oxytocin and placebo challenges on separate days; synthetic oxytocin (pitocin) or placebo was continuously infused over a 4-hour period. Eight subjects received oxytocin first, and seven received placebo first. The biological challenge procedures were described in Hollander et al (2003). Specifically, participants reported to the General Clinical Research Center where they spent the night before the challenge session; all participants fasted overnight. At 8:00 AM participants were awakened, and an indwelling intravenous catheter was inserted; vital signs were taken at 8:30 AM. At 9:00 AM, 6 cc³ of blood was drawn and participants were randomized in a double-blind fashion to receive intravenous oxytocin or placebo; just before the infusion, baseline assessment of the affective speech comprehension task was assessed. The initial vial of pitocin (10 U/mL) combined aseptically with a 1.01 bag of normal saline was first given at a rate of 10 mL/hour to minimize potential side effects and was gradually titrated up. The infusion rate was titrated every 15 min by 25 mL in the 1st hour, 50 mL in the 2nd, 100 mL in the 3rd, and held constant at 700 mL/hour during the 4th hour.

Comprehension of Affective Speech

Comprehension of affective speech was tested at baseline, just before the intravenous oxytocin/placebo infusion, and at 30, 60, 120, 180, and 240 min over the course of the infusion. The task used to assess comprehension of affective speech was based on one used by Heilman et al (1975), which revealed significant differences in affective speech comprehension between patients with right versus left temporoparietal lesions. Other researchers have also successfully used this task or a modified version of this task to assess affective speech comprehension (Adolphs and Tranel 1999; Adolphs et al 2001, 2002; Bowers et al 1987; Pihan et al 2000).

In the present investigation, participants were presented with four sentences of neutral content: "The boy went to the store," "The game ended at 4 o'clock," "Fish can jump out of the water," and "He tossed the bread to the pigeons." The sentences were pre-recorded and played for participants on a tape player; the voice reading the sentences was unknown to participants and was the same for all participants. Each sentence was presented with one of four emotional intonations (happy, indifferent, angry, and sad), with the pairing of emotional expression and sentences in 1 of 6 counterbalanced orders. Participants were then asked to indicate the emotional mood of the speaker by pointing to the word that corresponded to the emotion that they believed matched the one they heard on the tape; the examiner recorded participants' responses for all trials. As it turned out, this task was relatively easy for the adult participants in this study and, consequently, the findings were negatively skewed. In an effort to reduce the negative skew of the variable and to better balance the difficulty of the task, the outcome measure was scored dichotomously as 1 (all items correct) and 0 (not all items correct).

Statistical Analyses

We used mixed regression analyses to model the change in comprehension scores over time. This data analysis technique was chosen over the more traditional repeated measures ap-

proach for three reasons. First, traditional repeated measures analyses exclude subjects with incomplete data, which can result in loss of power and possible bias. By contrast, mixed regression models base estimates on all available data using maximum likelihood estimation, which enables one to make use of all data. In the present data set, although we were only missing 7 of the possible 180 observations, we would have had to eliminate all the data from 5 of the 15 subjects if we had used traditional repeated measures analysis of variance (ANOVA). Second, in this study each subject served as his or her own control, receiving both oxytocin and placebo; this design creates statistical dependency, and this dependency in observations can be accounted for in the mixed regression model. Finally, this analysis does not require strict assumptions about the error covariance matrix and is therefore more robust than repeated measures ANOVA.

We used the program MIXREG (Hedeker and Gibbons 1996) to perform the mixed regression analyses. In these analyses the linear trends in speech comprehension performance were estimated for each individual subject with all the available data across the time points for that subject. These individual linear trends were then used as the dependent variables in the analysis of the Time \times Treatment \times Order effects.

Results

As displayed in Figure 1, the mixed regression analysis revealed a significant three-way interaction of Time \times Treatment \times Order for the dichotomized comprehension of affective speech score ($z = -2.134$, $p = .033$, estimate = $-.170$). Subjects showed pretest to post-test improvement for three of the four Treatment \times Order conditions (i.e., Oxytocin First, Placebo First, Oxytocin Second), whereas for the Placebo Second condition, there was a slight drop in comprehension of affective speech from pretest to post-test (.958 to .898). This inconsistent pattern is most clearly driven by the finding that the second infusion placebo baseline scores were already high. Thus, subjects who received oxytocin first showed increased levels of retention in the task and did not show a tendency to revert to baseline when retested after a delay. By contrast, subjects who received placebo first did show a tendency to revert to baseline. The difference between the predicted pretest scores for subjects who received placebo second (.958) and placebo first (.712) is .246, which corresponds to a medium to large effect size (d) of .66.

It should be noted that one accidental confound due to experimental design was that subjects who received placebo first had, on average, a longer number of days between infusions than subjects who received oxytocin first. (The mean delay between infusions was 16.07 and the SD was 14.26 days.) To statistically control for this difference, we reran the mixed regression analysis with infusion lag time included as a covariate, and the three-way interaction of Time \times Treatment \times Order remained significant ($z = -2.131$, $p = .033$). Thus, even though the groups differed on lag time, this confound does not appear to be the basis for the difference in second baseline pretest performance.

Discussion

This study found that oxytocin administration facilitated the processing and retention of social information in adults diagnosed with autism or Asperger's disorder: compared with subjects who received placebo first, subjects who received oxytocin first showed increased retention of affective speech comprehension after a delay. These findings are similar to previous reports

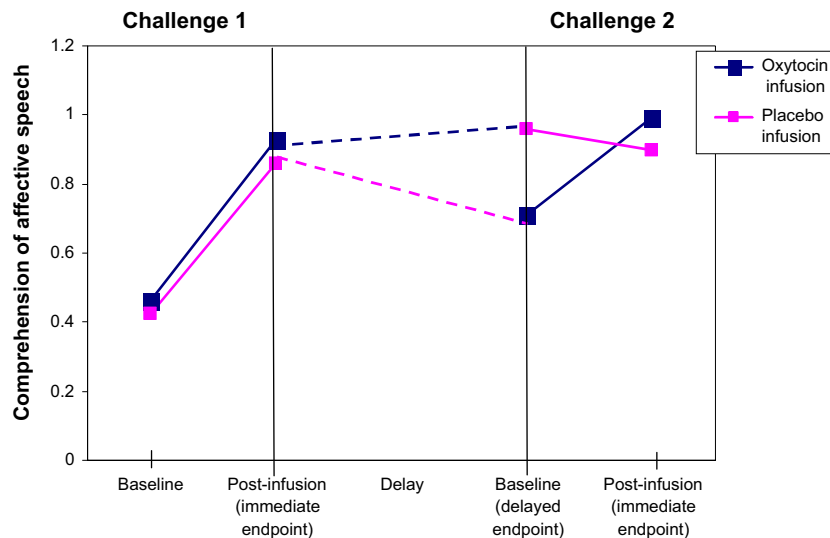


Figure 1. Estimated linear trends (on the basis of the mixed regression analysis) across time in the dichotomized scores of the affective speech comprehension as a function of condition (Oxytocin vs. Placebo) and order of administration (Oxytocin First vs. Placebo First). **Dotted line** represents interval between the first and second challenge procedures (days: mean = 16.07; SD = 14.26).

by our group in which oxytocin administration reduced repetitive behaviors in adults with autism or autism spectrum disorders (Hollander et al 2003); however, there was one noteworthy difference. The decrease in repetitive behaviors after oxytocin administration was a function of oxytocin and time; that is, there was an overall decrease in repetitive behaviors over time for those receiving oxytocin (Hollander et al 2003). By contrast, the increase in retention of social cognition after oxytocin administration was a function of oxytocin, time, and order. Specifically, three groups (Oxytocin First, Placebo First, and Oxytocin Second) improved from pretest to post-test on the affective speech comprehension task; however, those who received placebo first tended to revert to baseline during their pretest assessment after a delay (i.e., at the second challenge session), whereas those who received oxytocin first did not revert to baseline—that is, they appeared to retain the ability to accurately assign emotional significance to speech intonation. The fact that the differential carryover effects of oxytocin occur only for retention of social cognition but not for reduction of repetitive behaviors suggests that the relationship between oxytocin and retention of social cognition might be fairly complex.

These findings, although preliminary, are also consistent with studies investigating the effects of oxytocin and social recognition in rodents. Studies have shown that low doses of centrally or peripherally administered oxytocin increases social recognition in rodents (Popik et al 1992), and oxytocin antagonists disrupt social recognition in female rodents (Engelmann et al 1998). Moreover, studies with oxytocin knockout mice show that, compared with wild-type mice, mice lacking the oxytocin gene fail to recognize a conspecific over repeated exposures (Ferguson et al 2000), whereas oxytocin injections have been found to “rescue” their ability to acquire social memories (Ferguson et al 2001). Interestingly, the findings of Ferguson et al (2001) suggest that oxytocin specifically plays a role in memory acquisition but not in memory retrieval. Thus, in the present investigation, it might be that oxytocin administration is enabling autistic individuals to acquire and consolidate knowledge about the affective significance of speech intonation; of course, this hypothesis is purely conjecture at this point, but it would be an interesting issue to explore in future research. This research is also in accord with recent studies documenting the prosocial effects of oxytocin in humans. Kosfeld et al (2005) found that intranasal oxytocin increased trust among healthy male participants, and Kirsch et al

(2005) found that intranasal oxytocin dampened amygdala reactivity to threatening social stimuli. Although the current investigation did not specifically investigate this hypothesis, it might be that oxytocin reduces the anxiety and amygdala reactivity autistic individuals experience in relation to social situations (e.g., Dalton et al 2005), thus allowing them to attend to important social cues and to retain this information for future use. Conversely, in line with animal studies, oxytocin might play a more direct role in social memory acquisition. Again, future research will be needed to answer such questions concerning mechanism of action.

Although, as previously outlined, the findings from this study parallel those from a number of animal and human studies, there is one potential point of discontinuity from previous research. A handful of studies have explored the relationship between oxytocin and memory in humans. Although the findings from these studies have been inconsistent, with some studies finding effects (Bruins et al 1992; Fehm-Wolfsdorf et al 1984; Ferrier et al 1980) and others finding no effects (Fehm-Wolfsdorf et al 1988; Geenen et al 1988), the studies that have found effects have found that oxytocin inhibits performance on memory tasks. Indeed, Heinrichs et al (2004) recently investigated the effects of intranasal oxytocin on memory for words with reproductive or neutral content and found partial support for the selective amnesiac effects of oxytocin for reproductive-related words, suggesting that the relevance of the stimuli might interact with the effects of oxytocin. Although these findings seem to run counter to those in the present investigation, we believe there are important differences between the current investigation and these studies. Heinrichs et al (2004)—as well as the other studies that have looked at memory—investigated participants’ memory for words, whereas the present study investigated participants’ ability to accurately assign affective significance to speech intonation. Thus, whereas oxytocin might inhibit the ability to recall words from word-lists, it might yet facilitate more functional social information processing skills. Moreover, whereas these studies investigated healthy participants, the present study investigated autistic individuals who are known to have social deficits, and it might be that the therapeutic effects of oxytocin on social cognition are specific to those with deficits in this area—indeed, this parallels the findings from animals studies, in which the most clear-cut evidence for oxytocin facilitating social recognition was for mice lacking the oxytocin gene.

Although this study has a number of strengths including systematic diagnosis of autism and the use of a double-blind, placebo-controlled methodology, there were nonetheless some limitations. The participants in this study were somewhat heterogeneous, consisting of individuals diagnosed with autism and those diagnosed with Asperger's disorder; however, although these are two distinct disorders, the target outcome variable for this investigation was social cognition, and both groups are known to have deficits in this area. Participants were also somewhat heterogeneous with respect to age, ranging from 19 to 56 years. We do not see age variability to be a serious problem, however, because: 1) all participants were adults (i.e., combining children and adults would be more obviously problematic); and 2) the outcome variable is not known to be affected by age. More generally, to our mind, this heterogeneity, both in terms of diagnosis and age, should only undermine the ability to detect a significant effect. That said, future research should target specific subgroups to determine whether the effects of oxytocin administration on social cognition differ for those with autism versus those with other such autism spectrum disorders as Asperger's disorder. Similarly, future studies might want to investigate whether those with more severe social deficits benefit more (or less) from oxytocin administration. Another potential limitation concerns the measure for comprehension of affective speech; this test was fairly easy for the adult participants in this study, resulting in highly skewed scores and practice effects—indeed, it is likely that the ease of this test accounts for the improvement evidenced by those in the placebo condition. Thus, a follow-up study employing a more difficult affective speech comprehension test would be informative. Finally, because of the nature of the overall design of this study, there was a longer delay between the first and second infusion for subjects who received placebo first and oxytocin second. Although this delay provides a logical counter explanation for the obtained findings, it is important to keep in mind that we statistically controlled for lag time in our analyses, and the critical three-way interaction remained. Nevertheless, future studies to replicate this finding should experimentally rather than statistically eliminate this potential confound.

In conclusion, as noted at the outset, a number of researchers speculate that oxytocin likely plays a role in autism and autism spectrum disorders, especially with regard to the social deficits that characterize these disorders. To our knowledge, this is the first study to investigate the therapeutic effects of oxytocin on the social deficits in autism. The findings from this preliminary study are promising, and future research is needed to more thoroughly investigate this issue. It would be interesting to explore the effects of oxytocin on other aspects of social cognition—for example, face processing or making social attributions. Future research will also want to investigate whether different methods of administration (i.e., intranasal versus intravenous) yield different results and to investigate whether cerebrospinal fluid oxytocin levels differ depending on the method of administration used. Treatment studies with standardized measures to assess “real-life” improvements in social functioning are also needed to demonstrate the practical utility of oxytocin in the treatment of autism. Finally, studies are needed to investigate the effects of oxytocin administration in younger children who could potentially benefit from early intervention.

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