Plasma Oxytocin Levels in Autistic Children

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Background: *Social impairments are central to the syndrome of autism. The neuropeptide oxytocin (OT) has been implicated in the regulation of social behavior in animals but has not yet been examined in autistic subjects.*

Methods: *To determine whether autistic children have abnormalities in OT, midday plasma samples from 29 autistic and 30 age-matched normal children, all prepubertal, were analyzed by radioimmunoassay for levels of OT.*

Results: *Despite individual variability and overlapping group distributions, the autistic group had significantly lower plasma OT levels than the normal group. OT increased with age in the normal but not the autistic children. Elevated OT was associated with higher scores on social and developmental measures for the normal children, but was associated with lower scores for the autistic children. These relationships were strongest in a subset of autistic children identified as aloof.*

Conclusions: *Although making inferences to central OT functioning from peripheral measurement is difficult, the data suggest that OT abnormalities may exist in autism, and that more direct investigation of central nervous system OT function is warranted.* Biol Psychiatry 1998; 43:270–277 © *1998 Society of Biological Psychiatry*

Key Words: Autism, oxytocin, plasma, social deficits

Introduction

The most fundamental deficit in autism is impairment in face-to-face interaction skills. Most of the current diagnostic criteria for autism (American Psychiatric Association 1994; World Health Organization 1993) concern social and communication impairments. Although abnormal attachment per se is not a diagnostic criterion, a majority of young autistic children exhibit abnormal maternal or caretaker attachment interactions, ranging from aberrantly overattached to failure to discriminate caregivers from strangers (Howlin 1986; Rogers et al 1991; Shapiro et al 1987; Sigman and Mundy 1989). In addition, a majority of autistic children can be placed in one of three subtypes of social abnormality: aloof, passive, and active-but-odd (Dawson et al 1995; Volkmar et al 1993; Wing and Gould 1979). Another set of criterial symptoms for autism involves perseverative and ritualistic behavior (American Psychiatric Association 1994).

Animal studies have implicated the neuropeptide oxytocin (OT) in mammalian social bonding (Carter 1995; Insel 1992; Landgraf 1995; Newton 1978). OT, which is synthesized primarily in the hypothalamus, contributes to mammalian uterine contraction and lactation, and affects sexual bonding, maternal–infant bonding, and affiliative behavior (Carter et al 1995; Insel 1992; Landgraf 1995; Nelson and Panksepp 1996), although a recent study found that OT-deficient mice were capable of normal reproductive behavior (Young et al 1996). The specific mechanism of OT's regulation of behavioral bonding has not yet been determined. Insel (1992) suggested that OT may release social behavior sequences or may promote and reinforce social contact. Elevated OT in cerebrospinal fluid (CSF) has also been found in a subset of patients with obsessive–compulsive disorder (Leckman et al 1994), who show perseverative and ritualized behaviors.

Our group (Modahl et al 1992) hypothesized that abnormal OT system function might be found in autistic individuals, and suggested that localized dysfunction of OT receptor sites in limbic tissue could disrupt the perception of the significance of others, and disrupt normal affiliative behaviors (Waterhouse et al 1996). There is as yet no data on OT levels in autistic individuals, although abnormalities in plasma arginine vasopressin and B-endorphin have been reported (LeBoyer et al 1992). The present study was designed to measure OT levels in autistic children and normal controls, and to examine the association of OT levels and social behaviors in both groups. Since no data existed yet to confirm the hypothesis of altered OT function in autism, it was not considered justified or feasible to attempt direct CSF measurement; plasma levels were therefore used to provide an index of secretory activity. Abnormalities in plasma could then be

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Table 1. Sample Characteristics of Autistic and Normal Groups and Subgroups

	Normal (n = 30)	Autistic (n = 29)	Aloof subgroup (n = 10)	Active-but-odd subgroup (n = 13)
Age in months [mean (SD)]	106 (22)	97 (20)	94 (22)	103 (18)
Nonverbal IQ	105 (13)	61 (18)	49 (15)	72 (17)
Verbal IQ	111 (15)	54 (22)	38 (20)	66 (20)
Vineland Communication	105 (10)	60 (16)	51 (16)	69 (11)
Vineland Socialization	98 (14)	58 (11)	52 (8)	62 (10)
Vineland Daily Living	100 (11)	45 (14)	37 (12)	50 (15)

taken as preliminary confirmation of OT abnormalities, which would justify more direct central nervous system (CNS) measurements. In addition, if autism proves to be genetic, and if a point mutation interferes with OT gene expression, then plasma as well as central levels should be affected.

Methods and Materials

Subjects

Twenty-nine autistic and 30 nonautistic boys between the ages of 6 and 11 were recruited. Autistic and control subjects were group-matched for chronological age: autistic boys mean age = 8.1 years, SD = 1.7 years; control boys mean age = 8.8 years, SD = 1.8 years (see Table 1). The autistic sample was recruited from schools and autism support groups in the Massachusetts area. The control sample was recruited through advertisements in Connecticut and the Boston area. All subjects were compensated with a toy store gift certificate. All 29 autistic boys had received prior diagnoses of autistic disorder. For the current study, each child was diagnosed as meeting criteria for DSM-IV autistic disorder by a child neuropsychologist (DF); all records were then reviewed by a child psychiatrist (CF), who confirmed all diagnoses. Reports of symptoms were elicited by parent interview using a DSM-IV-based checklist (Wing Autistic Disorders Interview Checklist, Rapin 1996). Boys with prior diagnoses of infantile autism but meeting current criteria for pervasive developmental disorder not otherwise specified were excluded. Autistic girls were not recruited because the low rate of female subjects with autism made the recruitment of a sufficient sample size prohibitive in time and cost.

Inclusionary criteria for the boys recruited as normal controls included: 1) normal functioning in a regular grade school; 2) no known psychiatric conditions (as per parent interview); and 3) no known medical condition (as per parent interview). Parents of all subjects were questioned about the appearance of any voice changes, pubic hair, or face/body/underarm hair, and subjects evidencing any of these changes were excluded.

Procedure

All autistic subjects were tested at Boston Children's Hospital in Massachusetts. Six control subjects were tested at University of Connecticut Health Center, 13 were tested at Newington Children's Hospital in Connecticut, and 11 were tested at Boston Children's Hospital. Subjects were asked to fast 2 hours prior to the blood draw. Five subjects from each group were ascertained to have had snacks within 2 hours of the draw; the correlation of OT and time since food consumption is reported below. Blood draws were conducted for all subjects within 2 hours of noon, the time of peak pulsatile release of OT as determined by CSF measurement (Amico et al 1983). Ten cubic centimeters of blood were drawn from the arm by a qualified lab technician, collected into heparinized tubes, and iced until processing within 15 min. Samples were then centrifuged at 4°C at 3000 g for 20 min, after which plasma was separated into four tubes. Plasma was stored in a freezer at −70°C until overnight shipment, on dry ice, to the immunoassay lab for analysis. The peptide assay for OT was performed by Bowman Gray Immunoassay Laboratory (MM). The plasma samples were thawed on ice and aliquoted into 1-mL samples. Plasma proteins were precipitated with acetone, and the supernatant was extracted with petroleum ether. After lyophilization, the extracts were resuspended in assay buffer with duplicate measurements. 125I oxytocin was purchased from Dupont Inc (Boston, MA). A nonequilibrium assay was used with an incubation volume of 500 μL and an incubation time of 4 days at 4°C. The OT antisera, developed in the Bowman Gray Immunoassay Laboratory, is specific for the amidated peptide and was used at a final dilution of 1:300,000. There is no cross-reactivity with vasopressin or other related peptides. The ED_{50} of the assay was 2.8 pg as calculated using logit transformation of the data.

Tests Administered to All Subjects

All 59 boys were given three cognitive tests:

1. Stanford Binet 4th edition Copying subtest (Thorndike et al 1986). The Copying subtest requires children to copy presented designs, through reproduction of block arrangements and/or drawing. It contributes to the Stanford Binet index of visuospatial intelligence.
2. Stanford Binet 4th edition Pattern Analysis subtest. This subtest requires children to arrange patterned blocks to reproduce pictured designs or presented block arrangements. It also contributes to the Stanford Binet index of visuospatial intelligence.
3. Peabody Picture Vocabulary Test–Revised (PPVT-R) (Dunn and Dunn 1981). The PPVT requires children to

point to pictures in response to spoken words, and provides a measure of single-word receptive vocabulary.

Parent Interviews

All parents were given two interview questionnaires:

1. The Vineland Adaptive Behavior Scales (Sparrow et al 1984). Parents were interviewed in semistructured format about their children's daily living skills, communication, and socialization, including interpersonal relationships, play, and social coping skills.
2. Background Questionnaire. A brief questionnaire was developed for parents which requests information on variables that might affect OT level, including current medications, pubertal changes, mood state, emotional reaction to blood draw, exercise prior to the blood draw, and most recent food intake.

In addition, parents of the 29 autistic boys were interviewed with the following:

3. Wing Autistic Disorders Interview Checklist (in Rapin 1996). Parents of autistic children were interviewed with Wing's autism symptom checklist, based on DSM-III-R criteria (American Psychiatric Association 1987), and with an adapted version based on DSM-IV criteria (American Psychiatric Association 1994). Items survey a broad range of autistic symptoms, including specific impairments of social interaction and relations.
4. Wing's subtypes: criteria for aloof, passive and active-but-odd autistic social behavior classification (Wing and Gould 1979). All children were rated separately by two experimenters using these criteria. The experimenters agreed on 22 of the 29 autistic subjects; all 7 disagreements involved adjacent ratings. In these 7 cases, parents were recontacted and interviewed about specific behaviors to resolve the disagreement. This classification system has been found to produce valid and reliable subgroupings of autistic children (Castelloe and Dawson 1993; Dawson et al 1995; Volkmar et al 1989, 1993; Waterhouse et al 1996).

Table 2. Levels of Plasma OT in Autistic and Normal Children (pg/mL)

	Autistic (n = 29)	Normal (n = 30)
Mean (SD)	0.64 (0.58)	1.16[a] (0.77)
Median	0.45	1.06
Range	0–2.48	0–2.72

[a] $t = 3.0$, $p < .004$.

Results

Sample Characteristics

Descriptive statistics for background variables are provided in Table 1. The groups were well matched for chronological age. The control group showed significantly higher scores in nonverbal IQ, verbal IQ, and Vineland Communication, Socialization, and Daily Living standard scores than the autistic group.

Group Differences

Descriptive statistics and group differences for OT levels are presented in Table 2. Subjects with levels that were below the level of detection by radioimmunoassay were interpreted as having negligible amounts of plasma OT, and were coded as having 0 pg/mL; there were 3 such normal subjects and 6 such autistic subjects.

There was a significant difference in OT level between groups ($t = 3.00$, $p < .004$). Although the distributions were largely overlapping (Figure 1), the autistic group showed a greater number of nondetectable levels, somewhat less variability, and a lower central tendency than the control group.

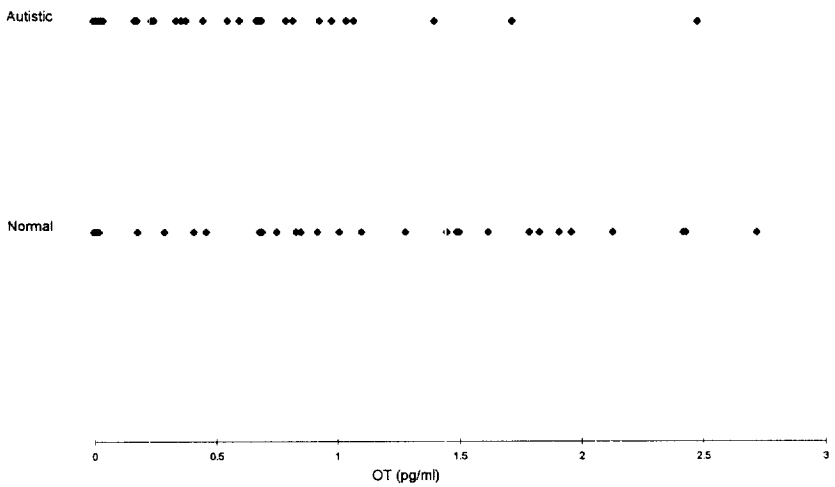

Figure 1. OT values for autistic and normal groups.

Table 3. Pearson Correlations by Group: OT with Physiological Factors

	Normal	Autistic
Age	.46[a]	−.14
Respiratory condition	−.34[b]	.04
Time of blood draw	−.31[b]	−.07
Time of waking	−.21	−.05
Peak exercise activity	−.32[b]	.11
Time since eating	−.36[c]	−.27
Mood	.04	−.23
Emotional reaction	−.17	.16

[a] $p < .01$.
[b] $p < .10$ (trend).
[c] $p < .05$.

Relationship of OT to Other Variables

Relationships between plasma OT levels and physiological factors are presented in Table 3. OT was positively associated with age for normal children, but not for autistic children. In normal children, OT was also negatively associated with amount of time before the blood draw that food was consumed, and there were trends for relationships between OT and the presence of a respiratory condition, peak level of physical exercise that day, and time of blood draw, in units of military time (i.e., 12:00, 13:00 hours). None of the physiological variables was significantly related to OT for the autistic group. Other factors that might affect OT level (time of waking, mood, and emotional reaction to the blood draw) showed no relationship with OT for either group.

Since 10 of the autistic children were on a variety of medications (4 on combinations and 6 on individual medications), they were individually examined for OT values that might be notably high or low. Four children were on clonidine; 2 of these were one SD below the autistic mean, and 2 were at the autistic mean. Two children were on Depakote; 1 was at the autistic mean, and 1 was one SD below the mean. One child was on Haldol; he was at the autistic mean. Two children were on Ritalin; 1 was one SD below the autistic mean, and 1 was one SD above the mean. One child each was on Tegretol and Dilantin; the first was at the autistic mean, and the second was one SD below the mean. Two children were on fluoxetine, 1 on imipramine, and 1 on amitriptyline; the latter was 0.75 SD below the autistic mean, and the others were at the autistic mean. Although children on medication therefore had somewhat lower OT values (0.48 on medication, 0.72 off medication), t tests showed no significant differences between OT values, or between IQ scores, for those children on or off medication. Thus, although more values were below than above the mean for medicated children, there appear to be no consistent or extreme effects of specific medications on OT plasma values.

Table 4. Pearson Correlations by Group: OT with Intellectual and Behavioral Scores

	Normal	Autistic
Nonverbal IQ	−.05	−.27
Verbal IQ	.08	−.29
Vineland scores		
Communication	.03	−.34[a]
Receptive	Ceiling effects	−.23
Expressive	−.36[b]	−.20
Written	.19	−.40[b]
Daily Living	.44[b]	−.36[b]
Personal Care	.46[b]	−.36[b]
Domestic	.20	−.30
Community	.44[c]	−.39[b]
Socialization	.32[a]	−.16
Interpersonal	.44[c]	−.34
Play	.04	−.18
Social Coping	.31[a]	−.28
Adaptive Level	.38[b]	−.33[a]
Total autistic symptoms		−.17

[a] $p < .10$ (trend).
[b] $p < .05$.
[c] $p < .01$.

Relationships between OT and intellectual and behavioral scores were also examined (see Table 4).

OT was not related to intellectual level for either the normal or the autistic group. All of the relationships between OT and the behavioral variables were in the negative direction for the autistic group and in the positive direction for the normal group (with the exception of expressive language). For the normal children, OT was positively associated with Vineland standard scores for Interpersonal Relationships, Daily Living Skills, Personal Care, Community Skills, and Adaptive Behavior Composite, and tended to be associated with Social Coping and overall Socialization. Within the autistic group, OT was negatively associated with Daily Living Skills, Personal Care, and Community Skills, and tended to be negatively associated with Written Language, overall Communication, Interpersonal Relationships, and overall Adaptive Level.

Because the Socialization domain was most theoretically related to OT functioning, relationships between OT and individual socialization items from the Vineland were explored. Significant relationships were found for a number of items. In normal children, OT was related consistently in the positive direction to socialization items, specifically to items regarding mastery of social conventions (correlations with OT: apologizes for mistakes, $r = .39$, $p < .05$; responds appropriately to introductions, $r = .38$, $p < .05$; ends conversations appropriately, $r = .53$, $p < .01$). For autistic children, OT was significantly *negatively* related to socialization items, with items relating to imitation showing the strongest association with OT

(correlations with OT: plays with household object, $r = -.48$, $p < .01$; imitates actions, $r = -.67$, $p < .0001$; delayed imitation of complex acts, $r = -.60$, $p < .001$; imitates phrases, $r = -.47$, $p < .05$; responds appropriately to introductions, $r = -.45$, $p < .01$). Trends in the same direction were found for laughs/smiles to praise, prefers some friends over others, has a preferred friend of the same sex, addresses others by name, and apologizes for mistakes.

Several items on the autistic symptom checklist correlated significantly with OT. Most strongly related was lack of imitation ($r = .61$, $p < .001$). Also significantly related to OT were lack of modesty ($r = .49$, $p < .01$) and no appropriate personal barriers ($r = .49$, $p < .01$). In the opposite direction, lower OT was associated with pronoun reversal ($r = -.39$, $p < .05$) and inappropriate conversation ($r = -.43$, $p < .01$), probably because only the higher functioning autistic children had enough language to show these symptoms.

Autistic children were rated using Wing's typology, and classified as "aloof," "passive," or "active-but-odd." Passive children were dropped from subsequent analyses because of insufficient sample size ($n = 6$). The aloof and active-but-odd groups differed significantly in nonverbal IQ, verbal IQ, number of social deficits on the autism symptom checklist, and in Vineland Communication, Socialization, and Daily Living Skills scores (see Table 1 for subgroup characteristics). There were also trends for significant differences in total number of autistic symptoms, and in number of "restricted repertoire" behaviors $p < .10$). In all cases, the aloof children were lower functioning and showed more symptoms. The groups did not differ significantly in OT level (aloof mean = 0.79, SD = 0.75, range = 0–2.48; active-but-odd mean = 0.61, SD = 0.53, range = 0–1.72).

Correlations between OT and physiological variables were calculated by Wing subgroup. One significant correlation (OT with mood, $r = -.65$, $p < .05$) was found only within the aloof autistic group.

Correlations between OT and intellectual and behavioral variables for each Wing subgroup are shown in Table 5.

For the aloof group only, OT showed consistently negative relationships with developmental and cognitive scores.

Relationships between OT and Vineland socialization items and between OT and autistic symptoms were explored for each Wing subgroup. Correlations involving single items and a small sample are of limited stability. It is noteworthy, however, that a consistent pattern emerged in the aloof group for social variables, with the highest correlations occurring for imitative behavior. Variables that correlated with OT at the $p < .01$ level were:

Table 5. Correlations for Aloof and Active-but-Odd Autistic Children: OT with Intellectual and Behavioral Scores

	Aloof	Active-but-odd
Nonverbal IQ	−.56	−.11
Verbal IQ	−.52	.05
Vineland scores		
Communication	−.70[a]	−.11
Receptive	−.71[a]	.01
Expressive	−.79[b]	−.17
Written	−.73[a]	−.17
Daily Living	−.69[a]	−.11
Personal Care	−.68[a]	−.30
Domestic	−.68[a]	−.01
Community	−.74[b]	−.10
Socialization	−.53	.02
Interpersonal	−.73[b]	.19
Play	−.62[a]	.06
Social Coping	−.71[a]	−.02
Adaptive Level	−.67[a]	−.10

[a] $p < .05$.
[b] $p < .01$.

Vineland socialization items: interacts with other children, $r = -.79$; imitates actions, $r = -.88$; delayed imitation, $r = -.83$; verbal imitation, $r = -.83$; prefers certain friends, $r = -.76$; identifies people by characteristics other than name, $r = -.79$; shares toys, $r = -.75$;

Autistic symptoms: seeks comfort mechanically, $r = .79$; no imitation, $r = .79$; self-injury, $r = .79$; restricted interests, $r = -.77$; no personal barriers, $r = .79$.

Stepwise regression analyses were conducted to determine whether OT independently accounted for variance in behavioral variables over and above verbal IQ and nonverbal IQ. Results suggested that a majority of OT's contribution to the variance was shared with verbal IQ and nonverbal IQ, although it did make significant unique contributions to variance in Interpersonal Relationships (OT semi-partial correlation (sr^2) = .09, $p < .02$; verbal IQ $sr^2 = .84$, $p < .0002$; nonverbal IQ, ns) and in Communication (OT $sr^2 = .06$, $p < .01$; verbal IQ $sr^2 = .91$, $p < .0001$; nonverbal IQ, ns). Nearly all of the variance contributed by OT to Daily Living and adaptive behavior scores was shared with verbal IQ and nonverbal IQ (OT did not meet significance for entry to these models).

Discussion

Summary of Results

Autistic children as a group showed lower OT levels than normal children, and failed to show the same pattern of

associations between OT and developmental and physiological factors, most notably, chronological age. For normal children, higher OT corresponded with greater interaction skill and daily living skills, independent of age. For the autistic group as a whole and for the aloof subgroup, higher OT correlated with deficits in these areas. The active-but-odd subgroup showed very few relationships between behavioral variables and OT, but those that did appear were in the same direction as for the total autistic group. Intellectual level was not associated with OT in normal children. Verbal and nonverbal IQ were modestly negatively related to OT in the aloof autistic subgroup and accounted for a majority of variance in behavior in this subgroup.

Group Results for OT Levels

Distributions of OT levels in both the normal and autistic groups revealed a significant number of nondetectable readings (3 normal, 6 autistic). The finding of nondetectable readings in these subjects appears to be reliable; reanalysis of their samples revealed levels that were near zero or nondetectable, consistent with initial findings. Despite considerable variability in OT levels for both groups, a significant group difference was obtained, in which OT level was lower in autistic children. This finding supports the hypothesis of altered OT in autistic children.

Relationship between OT and Physiological Variables

Further support for altered OT function in autism was the finding that autistic children failed to show the same pattern of relationships between OT and several basic physiological variables, especially age, that were characteristic of normal children. The apparent rise in OT with age is consistent with other hormone systems that surge before the onset of puberty. The failure of autistic children to display this effect for OT may reflect delays in physical development in this group (Campbell et al 1980; Simon and Gillies 1976). Modest trends in the data also indicated that normal children who had their blood drawn earlier in the day showed higher OT compared to those drawn later, suggesting a possible decrease in plasma level from 10:00 AM to 2:00 PM. This phenomenon was not present in the autistic children.

While prior reports indicate that OT release may be affected by stress (see Carter and Altemus 1997), the current study found no relationship between the degree or length of negative emotional reaction and OT. Future studies of OT should employ more sophisticated measures of physiological stress response and of related traits (e.g., anxiety sensitivity).

The OT system of the autistic child may be consistent with that of the normal child in one area: relation to food consumption. Although the correlation between OT and time since food consumption reached significance for normal children and not for the autistic children, there is no significant difference between the two correlations. The small amplifying effect of recent food consumption on OT might reflect a peripheral contribution to plasma OT level through gut response, which appears to be relatively intact in autistic children.

Relationship between OT and Developmental Variables

Normal children with more advanced interpersonal relationships tended to have higher plasma OT, but showed no association between OT and intellectual level. In autistic children, however, higher plasma OT levels are associated with more delayed social, language, and intellectual development. For autistic children, the three items most negatively related to OT were all imitation items. Social imitation is a fundamental component of social interaction, and is one of the primary, biologically determined bases of social behavior (Waterhouse et al 1996). Correlations between OT and items regarding specific social behaviors, however, should be interpreted with caution given their restricted range, nonnormal distributions, and the trichotomous nature of the variables.

Relationship between OT and Specific Autistic Symptoms

Greater deficits in social awareness were correlated with higher OT in autism. Greater autistic language deficits, however, were significantly correlated with lower OT. This may reflect the fact that only the higher functioning autistic children had enough spoken language for specific language abnormalities to appear.

Wing's Subtypes

Although absolute OT level did not differ significantly between aloof and active-but-odd subgroups, OT was associated with developmental variables for the aloof children but not the active-but-odd children. Although these correlations should be approached with caution due to limited sample sizes, strong and consistent patterns of relationships emerged. The aloof children showed OT-related deficits in all major domains of functioning measured by the Vineland, including the socialization subdomains of Interpersonal Relationships, Play, and Social Coping, with the highest correlations appearing for items related to imitation. Similarly, expression of autistic symptoms, particularly within the areas of imitation, play, and

the identification of emotions and peer-directed behavior, were associated with elevated OT in the aloof group. As with language abnormalities, the fact that restricted interests were associated with OT in the opposite direction probably reflects the fact that only the higher functioning children were described as having restricted patterns of interests.

In sum, higher levels of OT are significantly associated with poorer development of social and communication skills in aloof autistic children, but not in active-but-odd children. This finding suggests support for the distinction between two of Wing's types.

Conclusions

Despite mean differences in OT function between autistic and normal children, the respective distributions of OT levels largely overlapped. Thus it is possible to be autistic and express apparently normal OT levels, and it is possible to be normal with very low OT levels. OT production and release is obviously subject to great individual variability.

Despite lower OT in the autistic group, autistic individuals with higher OT levels were significantly more socially and developmentally impaired. The fact that the between-group and within-group differences are in opposite directions (if replicated on other samples) would suggest that a simple OT deficit model is inadequate. Measured abnormalities in plasma OT levels may be reflecting underlying disruptions in receptors or in substances upstream from OT, resulting in secondary OT dysregulation.

Making inferences about the central role of a peptide from plasma measurement is difficult. There are several possible mechanisms that could result in abnormal plasma OT levels, some of which do not involve central mechanisms. Plasma measurement of a peptide such as OT is a less sensitive measure of its central functioning than measurement in CSF. Changes in plasma and CSF OT levels in response to some stimuli may not be correlated (Amico et al 1990). Despite these limitations, abnormalities in hypothalamic OT production or release could be evidenced in plasma measurement. As noted above, if OT gene expression is abnormal in autism, this should affect plasma as well as central OT. In addition, there is constant and significant bidirectional passage of peptides, including OT, across the blood–brain barrier (Banks and Kastin 1992). Moreover, central peptides and peripheral peptides continuously influence one another's production through intermediary triggers in complex cascades (Begley 1994). The fact that current plasma OT measurements were not related to transient state changes in response to the situation, but were related to enduring psychological characteristics would seem difficult to explain solely with peripheral mechanisms.

Studies often use plasma measurement for preliminary examination of transmitter status in a psychiatric population (e.g., the well-documented finding of hyperserotonemia in autism; for review, see Fein et al 1996). Thus, the current findings should be viewed as a preliminary indication that OT may play a role in autism.

Another limitation of the current study is the use of only male subjects. Possible gender differences in OT (Insel et al 1991; Insel and Hulihan 1995) preclude generalization to female subjects.

Our explanations assume that the direction of causality for OT's involvement in autistic behavior proceeds from neural bases to behavior. It is also possible that, given a preexisting state of social disengagement because of a different neurological dysfunction, the autistic child may experience secondary changes in the OT system (Landgraf 1995).

OT's behavioral functions and patterns of release should be studied in a larger sample of normal children. Measurement of OT levels in CSF, and positron-emission tomography studies of central OT receptor distribution would be more direct tests of the role of OT in autism.

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References

American Psychiatric Association (1987): *Diagnostic and Statistical Manual of Mental Disorders,* 3rd ed rev. Washington, DC: American Psychiatric Press.

American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. Washington, DC: American Psychiatric Press.

Amico JA, Tenicela R, Johnston J, Robinson AG (1983): A time dependent peak of OT exists in cerebrospinal fluid but not plasma of humans. *J Clin Endocrin Metab* 57:947–951.

Amico JA, Challinor SM, Cameron JL (1990): Pattern of oxytocin concentrations in the plasma and cerebrospinal fluid of lactating rhesus monkeys (Macaca mulatta): Evidence for functionally independent oxytocinergic pathways in primates. *J Clin Endocrinol Metab* 71:1531–1535.

Banks WA, Kastin AJ (1992): Bidirectional passage of peptides across the blood-brain barrier. *Prog Brain Res* 91:139–148.

Begley DJ (1994): Peptides and the blood-brain barrier: The status of our understanding. *Ann NY Acad Sci* 739:89–100.

Campbell M, Petti TA, Greene WH, Cohen IL, Genieser NB, David R (1980): Some physical parameters of young autistic children. *J Am Acad Child Psychiatry* 19:193–212.

Carter CS, Altemus M (1997): Integrative functions of lactational hormones in social behavior and stress management. *Ann NY Acad Sci.*

Carter CS, DeVries AC, Getz LL (1995): Physiological substrates of mammalian monogamy: The prairie vole model. *Neurosci Biobehav Rev* 19:303–314.

Castelloe P, Dawson G (1993): Subclassification of children with autism and pervasive developmental disorder: A questionnaire based on Wing's subgrouping scheme. *J Autism Dev Disord* 23:229–241.

Dawson G, Klinger L, Panatiotides H, Lewy A, Castelloe P (1995): Subgroups of autistic children based on social behavior display distinct patterns of brain activity. *J Abnorm Child Psychol* 23:569–583.

Dunn LM, Dunn L (1981): Peabody Picture Vocabulary Test–Revised. Circle Pines MN: American Guidance Service.

Fein D, Joy S, Green L, Waterhouse L (1996): Autism and pervasive developmental disorders. In: Fogel B, Schiffer R, Rao S, editors. *Neuropsychiatry.* Baltimore: Williams & Wilkins, pp 571–614.

Howlin P (1986): An overview of social behavior in autism. In: Schopler E, Mesibov GB, editors. *Social Behavior in Autism.* New York: Plenum Press, pp 103–126.

Insel TR (1992): OT—A neuropeptide for affiliation. *Psychoneuroendocrinology* 17:3–35.

Insel TR, Hulihan TJ (1995): A gender-specific mechanism for pair bonding: Oxytocin and partner preference formation in monogamous voles. *Behav Neurosci* 109:782–789.

Insel TR, Gelhard R, Shapiro LE (1991): The comparative distribution of forebrain receptors for neurohypophyseal peptides in monogamous and polygamous mice. *Neuroscience* 43:623–630.

Landgraf R (1995): Morton Jones Memorial Lecture. Intracerebrally released vasopressin and OT: Measurement, mechanisms and behavioral consequences. *J Neuroendocrinol* 7:243–253.

LeBoyer M, Bouvard MP, Launay JM, Tabuteau F, Waller D, Dugas M, et al (1992): A double-blind study of naltrexone in infantile autism. *J Autism Dev Disord* 22:309–319.

Leckman JF, Goodman WK, North WG, Chappell PB, Price LH, Pauls DL, et al (1994): Elevated cerebrospinal fluid levels of oxytocin in obsessive-compulsive disorder. *Arch Gen Psychiatry* 51:782–792.

Modahl C, Fein D, Waterhouse L, Newton N (1992): Does oxytocin mediate the social deficits in infantile autism? *J Autism Dev Disord* 449–451.

Nelson E, Panksepp J (1996): Oxytocin mediates acquisition of maternally associated odor preferences in preweanling rat pups. *Behav Neurosci* 110:583–592.

Newton N (1978): The role of OT reflexes in three interpersonal reproductive acts: Coitus, birth and breast feeding. In: Carenza L, Pancheri P, Zichella L, editors. *Clinical Psychoneuroendocrinology in Reproduction: Proceedings of the Serono Symposia 22.* New York: Academic Press, pp 165–182.

Rapin I (Editor for the Autism and Language Disorders Collaborative Project: Preschool Study Group) (1996): *Preschool children with inadequate communication: Developmental language disorder, autism, mental deficiency. Clin Dev Med* 139.

Rogers S, Ozonoff S, Maslin-Cole P (1991): A comparative study of attachment behavior in young children with autism or other psychiatric disorders. *J Am Acad Child Adolesc Psychiatry* 50:483–488.

Shapiro T, Sherman M, Calamari G, Koch D (1987): Attachment in autism and other developmental disorders. *J Am Acad Child Adolesc Psychiatry* 26:480–484.

Sigman M, Mundy P (1989): Social attachments in autistic children. *J Am Acad Child Adolesc Psychiatry* 28:74–81.

Simon GB, Gillies SM (1976): Some physical characteristics of a group of psychotic children. *Br J Psychiatry* 110:104–107.

Sparrow SS, Balla DA, Cicchetti DV (1984): *Vineland Adaptive Behavior Scales.* Circle Pines, MN: American Guidance Service.

Thorndike R, Hagan E, Sattler JM (1986): *Stanford-Binet Intelligence Test,* 4th ed. Chicago: Riverside.

Volkmar FR, Cohen DJ, Bregman JD, Hooks MY, Stevenson JM (1989): An examination of social typologies found in autism. *J Am Acad Child Adolesc Psychiatry* 28:82–86.

Volkmar FR, Carter A, Sparrow SS, Cicchetti D (1993): Quantifying social development in autism. *J Am Acad Child Adolescent Psychiatry* 32:627–632.

Waterhouse L, Fein D, Modahl C (1996a): Neurofunctional mechanisms of autism. *Psychol Rev* 103:457–489.

Waterhouse L, Morris R, Allen D, Dunn M, Fein D, Feinstein C (1996b): Diagnosis and classification in autism. *J Autism Dev Disord* 26:59–86.

Wing L, Gould J (1979): Severe impairments of social interaction and associated abnormalities in children: Epidemiology and classification. *J Autism Dev Disord* 9:11–29.

World Health Organization (1993): *International Classification of Diseases,* 10th ed. Geneva: World Health Organization.

Young LJ, Wang Z, Nishimori K, Guo O, Matzuk M, Insel TR (1996): Maternal behavior and brain oxytocin receptors unaffected in oxytocin knockout mice. Paper presented at Society for Neuroscience, Washington DC.