Pitocin and Autism Spectrum Disorder

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Lay Abstract

People with autism spectrum disorder (ASD) have difficulty interacting and communicating with other people and have a restricted range of interest and behavior. Oxytocin (OT) is a chemical messenger in the brain that plays an important role in many of the social emotional processes that are deficient in ASD, such as reading the emotions of others, forming relationships and reducing anxiety in social situations, suggesting a relationship between ASD and some malfunction of OT. Although the cause of ASD is not yet understood, it is believed to involve an interaction between an inherited vulnerability and an environmental trigger. Animal studies have shown that early exposure to excess OT can interfere with social emotional processes and OT function later in life. The current study explores a possible link between ASD and the use of pitocin - a synthetic form of OT – to induce or speed up labor. We looked at the birth histories of 173 children who were seen for neuropsychological evaluation of school difficulties, and found that the rate of exposure to OT during delivery was significantly higher for children diagnosed with ASD (55%) than for children with attention deficit/hyperactivity disorder (ADHD; 39%), anxiety or depression (PSY; 18%), or specific cognitive processing deficits (COG; 27%). In addition, the rate of OT exposure for girls with ADHD was significantly higher than for girls in the other groups. These results suggest that the use of pitocin in labor increases the risk for ASD and ADHD in some children, perhaps by interfering with the development of the brain circuits that process social emotional information.

Scientific Abstract

A growing body of evidence from multiple lines of research points to a central role for the neuropeptide oxytocin (OT) in autism spectrum disorder (ASD). There is also evidence that early exposure to exogenous OT can disrupt OT function and social behavior later in life, pointing to OT as a possible environmental trigger in the etiology of ASD. A possible source of such exposure is the use of synthetic OT (pitocin) for the induction and augmentation of labor, a practice that has increased dramatically in recent decades, in parallel with the increased incidence of ASD. A small number of studies have explored this link, with inconsistent results. Subjects in the current study were 173 children, aged 6 to 16, seen for neuropsychological evaluation of school-related difficulties. The rate of pitocin exposure was significantly higher for children with ASD (54.8%; 23/42) than for children with attention deficit/hyperactivity disorder (ADHD) (39.3%; 24/61), anxiety or depression (PSY; 18.2%; 10/55), specific cognitive processing deficit (COG) (26.7%; 4/15), and the general population (22.5%). An unexpected finding was that the rate of OT exposure in girls with ADHD was also significantly increased (61.5%; 16/26). These findings point to increased risk for ASD in boys and ADHD in girls with the use of pitocin during labor. The results are discussed in terms of disruption of the closely related but sexually dimorphic neuropeptides OT and arginine vasopressin (AVP).

Key words: ADHD, autism spectrum disorder, labor induction, oxytocin, pitocin, vasopressin

Introduction

A growing body of evidence from multiple lines of research points to a central role for the neuropeptide oxytocin (OT) in autism spectrum disorder (ASD) (see for review Bartz and Hollander, 2006; Carter, 2007; Hammock and Young, 2006; Marazziti and Dell'Osso, 2008). In addition to its hormonal action in the initiation of labor and lactation, the importance of OT in the central control of social affiliative behaviors and social emotional processes has been well established in both animals and humans (see for review Campbell, 2008; Donaldson and Young, 2008; Heinrichs *et al.*, 2009; Neumann, 2008; Ross and Young, 2009). Animal studies examining the patterns of endogenous OT release, the distribution of OT receptors in the brains of species differing in sociality, and the effects on behavior of manipulation of the central availability of OT - via local administration of OT or OT antagonists and genetic knockout of OT or the OT receptor, demonstrate its involvement in maternal care, pair bonding, social memory, and decreased stress response.

In humans, endogenous release of OT is associated with stress reduction and feelings of relaxation (Altemus *et al.,* 1995; Heinrichs, *et al.,* 2001), and intranasal administration of OT has been shown to facilitate the processing of social emotional information. Specifically, improved perception of emotion in facial expression (Di Simplicio *et al.,* 2009; Domes *et al.,* 2007a), increased gaze to the eye area (Guastella *et al.,* 2008a), improved memory for faces (Guastella, *et al.,* 2008b; Rimmele *et al.,* 2009), and increased positive communication in couples (Ditzen *et al.,* 2009), have been demonstrated. Administration of OT has also been shown to decrease social anxiety, as indicated by increased trust (Baumgartner *et al.*, 2008; Kosfeld *et al.*, 2005)

and by decreased emotional and physiological response to social stress or anxiety (Heinrichs *et al.,* 2003; Kirsch *et al.,* 2005).

ASD is characterized by deficits in many of these same OT-mediated social emotional processes (American Psychiatric Association, 1994), leading a number of researchers to propose a link between ASD and dysfunction of the OT neural system (Carter, 2007; Heinrichs and Domes, 2008; Insel *et al.*, 1999; Lim *et al.*, 2005; Modahl *et al*., 1992; Panksepp, 1993, Welch and Ruggiero, 2005). Increasing support for this link has been provided by genetic studies demonstrating an association between ASD and polymorphisms in the gene for the OT receptor (Gregory *et al.,* 2009; Jacob *et al.*, 2007; Wu *et al.*, 2005), by evidence of abnormal metabolism of OT in ASD (Green *et al.,* 2001; Modahl *et al*., 1998), and by a small number of treatments studies demonstrating decreased deficits in individuals with ASD with the administration of OT (Bartz and Hollander, 2008; Guastella *et al*., 2009; Hollander *et al.,* 2003; 2007).

Also important is evidence that early exogenous exposure to OT can result in disruption of both OT and social behavior later in life (Carter *et al.,* 2008; 2009), suggesting that a similar exposure in humans could increase the risk for ASD. The etiology of ASD is believed to involve an interaction between genetic vulnerability and exposure to an environmental trigger very early in life. A possible source of such exposure is the use of synthetic OT (pitocin) for the induction and augmentation of labor, a practice that has increased dramatically in recent decades, in parallel, it can be argued, with the increase in ASD. The rate of induction of labor in the US more than doubled between 1990 and 2006, from 9.5% of all births to 22.5% (Martin, et al., 2009). The rate of ASD in the US in 2006 was an alarming 0.9% (1 in 110 children eight years

of age), which represents an increase of nearly 60% since 2002 (Centers for Disease Control and Prevention, 2009), and a roughly 10-fold increase since the 1980s (Blaxill, 2004), for which improved awareness and identification may not fully account. Several authors have expressed concern that OT exposure during labor may increase the risk for ASD in individuals with genetic vulnerability (Carter *et al.*, 2008; Hollander *et al.,* 1998; Wahl, 2004). Hollander *et al*. (1998) suggested that the presence of excess OT in the fetal brain may result in the down-regulation of the OT receptor. While the maternal-placental barrier and the fetal blood-brain barrier are presumed to protect the baby from OT exposure, there is evidence that this protection is not complete (Wahl, 2004).

A small number of studies have explored this possibility, examining the rate of labor induction or exposure to pitocin in children with autism, with inconsistent results. Hollander *et al.* (1998) found that of 54 autistic patients (age and gender unspecified), 61% had a history of labor induction with pitocin, a much higher percentage than the national rate of 20 to 25%. Fein *et al.* (1997) reviewed data from an earlier study of 633 preschool children seen for evaluation of communication deficits (Rapin, 1996). Birth history regarding labor induction was known for 455 children (gender unspecified), and the rate of labor induction was found to be very close to the expected rate in each of four groups: children with developmental language disorders (19.3%; n=197); high functioning autism (21.6%; n=51), low functioning autism (24.4%; n=123), and generalized low IQ (27.1%; n=107). A subsequent study by Gale *et al*. (2003) comparing 41 boys (aged 6 to16 years) with autistic disorder, with 25 age- and IQ-matched boys without autism (15 typically developed; 10 with mental retardation), found no difference in labor induction with pitocin as a function of either diagnosis (autism 29% versus controls 32%) or IQ.

Possible factors contributing to the inconsistency in findings include differences in the age, gender and symptom severity of the subjects. Also, while these studies involved individuals with autism, the trend in recent years is toward a view of the disorder as comprising the full range of symptom severity, as reflected in proposed changes to the diagnostic criteria (American Psychiatric Association, 2010). As pointed out by Muhle *et al*. (2004), the genetic vulnerability to ASD involves a number of different genes, each controlling different characteristics, and genetic concordance is significantly higher for the full autism spectrum, representing the broader phenotype, than for classic autism (92% versus 60% for monozygotic twins). This suggests that any relationship between ASD and a particular epigenetic or environmental factor, such as exogenous OT, may also be stronger in a population representing the full autism spectrum. The current study examines the rate of exposure to exogenous OT (pitocin) during labor in a group of children with ASD, generally with milder deficits, as compared with children with other neurodevelopmental conditions.

Methods

Subjects were children seen for neuropsychological evaluation of school-related difficulties in a private practice setting in a New York City suburb during a ten-year period (January 2000 through December 2009). Children were included who were 6 through 16 years of age with no history of brain injury and no concurrent medical illness, and for whom the birth history was available and reliable. Information regarding pregnancy and delivery was obtained through parent interview and a parent-completed history questionnaire. Children were seen over three visits for clinical interview and administration of standardized neuropsychological measures,

which included either the WISC-III (Wechsler, 1991) or the WISC-IV (Wechsler, 2003), and either the Beck Youth Inventories (Beck et al., 2001), or for children older than fourteen, the Millon Adolescent Clinical Inventory (Millon, 1993). Diagnosis was based on DSM-IV criteria (American Psychiatric Association, 1994).

Results

Subjects included in the study were 173 children (55 girls), with a mean age of 11.1 years and mean Full Scale IQ of 103. Subjects were assigned to one of four diagnostic groups. Subjects in the ASD group (n=42, 1 girl) met criteria for autism, pervasive developmental disorder not otherwise specified (PDD NOS) or Asperger syndrome. Subjects in the ADHD group (n=61, 26 girls) met criteria for attention deficit/hyperactivity disorder, and subjects in the PSY group (n=55, 19 girls) were children diagnosed with an anxiety or depressive disorder. Subjects in the COG group (n=15, 9 girls) were those who did not meet criteria for a psychiatric diagnosis but demonstrated a specific cognitive (auditory verbal or visual spatial) processing deficit and/or visual motor coordination deficit to which their difficulties could be attributed.

In the ASD group, 54.8% had a history of OT exposure at birth, a rate higher than that of the ADHD (39.3%), PSY (18.2%) or COG (26.7%) groups. Analysis by Pearson Chi-Square demonstrates a significant relationship between OT exposure and diagnosis ($X^2 = 13.714$ {df3}; $p = 0.003$). The rate of OT exposure in the ASD group is also much higher than that of the general population (22.5% in 2006), as well as the rate for the non-Hispanic white population (26.7%), from which the current study sample is largely drawn. There was no between group

difference in age, but analysis of variance revealed a small but significant (p = 0.036) group difference in average Full Scale IQ: ASD 99; PSY 101; COG 103; ADHD 105.

Because of the very low rate of ASD (1 in 55) among the girls in this sample, the analyses were repeated for each gender group separately. For the male subjects, the same results were seen – OT exposure was significantly higher for those with ASD than for those in the other groups. Analysis of the data from the female subjects revealed an important and unexpected finding. For girls, the rate of OT exposure in the ADHD group (61.5%) was significantly higher than that of the PSY (15.8%) and COG (22.2%) groups. For boys, the rate of OT exposure in the ADHD group (22.9%) was not elevated relative to the other groups (PSY 19.4%, COG 33.3%). (See Table 1).

		ASD	ADHD	PSY	COG		X^2
Boys (n = 118)		**53.7**	**22.9**	**19.4**	**33.3**		**12.525**
		22/41	8/35	7/36	2/6		(p = .006)
Girls (n = 55)		**100**	**61.5**	**15.8**	**22.2**		**10.185**
		1/1	16/26	3/19	2/9		(p = .017)
Total (n = 173)		**54.8**	**39.3**	**18.2**	**26.7**		**13.714**
		23/42	24/61	10/55	4/15		(p = .003)

TABLE 1: PERCENT OT EXPOSURE BY GROUP

Discussion

These results provide clear support for an increased risk of ASD with the administration of pitocin during labor among boys. The rate of OT exposure in the ASD group in the current study (55%) is similar to that found by Hollander *et al.* (1998) in a group of autistic individuals (61%).

Two other studies, however, found no relationship between OT exposure and autism. Fein *et al.* (1997) reported labor induction rates of 21.6% and 24.4% in children with high- and low-functioning autism (23.6% for the two groups combined), and Gale *et al.* (2003) reported an OT exposure rate of 29% in an autism group and 32% in a control group. These rates were not increased relative to an expected rate of 20 to 25%. Possible sources of inconsistency in the findings include differences in the age, gender, and symptom severity of the subjects. The diagnosis of autism may be less reliable at very young ages (Blaxill, 2004), as were the subjects in the Fein *et al.* study. Early exogenous exposure to OT may have a different effect in males and females (Carter *et al.,* 2008) - the Hollander *et al.* and Gale *et al*. studies involved only male subjects and gender was unspecified in the Fein *et al.* study - or may be associated with a feature of ASD that is more characteristic of the higher end of the autism spectrum.

Another possibility is that the rates of OT exposure in these autism groups are in fact elevated when compared with the population rate at the time that the subjects were born. As noted above, the rate of labor induction in the US was 9.5% in 1990, and had increased sharply, to 20%, by 1999 (Martin *et al.,* 2009). Subjects in the Fein *et al.* (1997) study were 3 to 7 years of age and therefore born between around 1988 and 1992, and subjects in the Gale *et al*. (2003) study were 6 to 16 years of age, born between around 1986 and 1996. Even using for comparison an expected rate of 17% for 1996 (Martin *et al.*, 2009) - the birth year of the youngest subjects in the most recent study, the rates of labor induction and OT exposure in the autism groups in the Fein *et al*. and Gale *et al.* studies (23.6% and 29%) are significantly elevated ($p < 0.05$). Thus, data from all four studies points to an increased risk for ASD with the use of pitocin in labor.

The mechanism for this risk remains to be illuminated. It may be that the administration of pitocin to the mother during delivery results in excess OT in the fetal brain, causing the down-regulation of OT receptors, as proposed by Hollander *et al*. (1998). In support of this, Gregory *et al.* (2009) found decreased representation of the OT receptor in the temporal cortex of individuals with ASD. Neonatal manipulation of OT can cause long-term changes in brain OT, social emotional processes and the distribution of neuropeptide receptors (Carter *et al.,* 2008; 2009). In animals, the location of OT receptors in brain regions involved with reward (*e.g.* the nucleus accumbens) is associated with increased social affiliation (see for review Young *et al.*, 2008). In humans, administration of OT has been shown to decrease the autonomic response to fearful social stimuli (Heinrichs *et al.,* 2003; Kirsch *et al*., 2005). Disruption of OT function secondary to exposure to exogenous OT during labor may therefore contribute to social deficits in ASD by decreasing the reward value of social interaction and/or increasing social anxiety.

Another possibility is that the use of pitocin in labor affects the child indirectly by decreasing postpartum OT levels in the mother, interfering with maternal care and attachment. Jonas *et al.* (2009) found a dose-dependent decrease in OT levels as measured two days after birth in mothers who had pitocin infusion during labor. Feldman *et al.* (2007) demonstrated an association between plasma OT and positive interaction of the mother with the infant in the first postpartum month. Lack of maternal care or attachment early in life can have long-term effects on the OT system and on social development (Ross and Young, 2009). Winslow *et al.* (2005) found lower OT concentrations in the cerebrospinal fluid (CSF) of adolescent rhesus macaques that had been raised in a nursery by humans rather than by their mothers. Women with a history of early childhood neglect or abuse had significantly lower levels of OT in CSF than did women

without such experience (Heim, 2008), and men who had experienced early parental separation showed decreased sensitivity to the stress-reducing effects of intranasal OT (Meinlschmidt and Heim, 2007).

Exogenous postpartum OT in the infant could, by influencing feedback mechanisms, interfere with the endogenous release of OT in response to the mother's touch, along with its stress-reducing effects. Both OT release and stress reduction increase with positive physical contact (Ditzen *et al*., 2009), and OT increases the stress-protective effects of touch (Heinrichs *et al*., 2003). The soothing effect on a baby of being touched and held likely operates by stimulating the release of OT in the infant's brain, reducing anxiety, distress and crying. This early sensory activation of the OT system may be necessary for its subsequent development, as is true for other sensory neural systems. A reduction in the OT-mediated reward value of touch may help explain the hypersensitivity to touch associated with ASD (American Psychiatric Association, 1994). OT may also mediate the reward value for the baby of other social emotional stimuli and responsive behaviors, such as making eye contact and exchanging smiles with the mother and babbling in response to her voice, which are likely necessary for the development of visual and auditory processing of emotion and communication, processes that are characteristically deficient in ASD.

At the same time, reducing distress in the baby is highly rewarding for the mother, whereas failure to do so increases her distress and anxiety. This in turn can interfere with maternal care, including breastfeeding (Zanardo, 2009), depriving both mother and baby of the stress-reducing effects of nursing and the regular close physical contact it ensures (Heinrichs *et al.,* 2001; Uvnäs-

Moberg, 1996). The OT-mediated calming effects on mother and baby are thus mutually reinforcing, and disruption of postpartum OT function in either the infant or the mother at this critical time is likely to interfere with mother-infant bonding and the subsequent development of the baby's OT system and social emotional processing later in life.

The social emotional deficits in ASD may also reflect the disruption of another neuropeptide - arginine vasopressin (AVP), which is closely related to OT both chemically and functionally and has also been associated with both social emotional processes and ASD (see for review Donaldson and Young, 2008; Heinrichs *et al*., 2009). In addition, Carter *et al.* (2009) demonstrated that early exogenous OT can influence the development of the AVP system. OT and AVP are sexually dimorphic; OT is central to female-specific (maternal) behaviors (see for review Campbell, 2008) and AVP to male-specific behaviors, specifically inter-male and territorial aggression (see for review Caldwell *et al.,* 2008; Young *et al*., 2008). Social interaction among boys is largely competitive, and, like play fighting in young animals, may involve brain systems associated with aggression. Thus, reduced availability of AVP may play a role in the social deficit of boys with ASD.

Social interaction among girls, however, is more typically affiliative, and may be less affected by reduced availability of AVP. This may help explain the unexpected finding of a high rate of OT exposure in girls with ADHD in the current study, pointing to an increased risk for girls for ADHD with the use of pitocin in labor. This finding may reflect the lack of an observable social deficit in the girls at the higher end of the autism spectrum (only 1 of 55 girls met diagnostic criteria for ASD), rather than the lack of an attention deficit in the boys. Attention deficits are

common in ASD, and considerable clinical and genetic overlap between ASD and ADHD is well documented (see for review Rommelse, *et al.,* 2010; Sinzig *et al.*, 2009), but current diagnostic criteria (DSM-IV) do not allow for a diagnosis of ADHD in individuals with ASD (American Psychiatric Association, 1994). In the current study, there was no difference in the rate of attentional difficulties in the classroom for boys with ASD (78%), boys with ADHD (71%), or girls with ADHD (72%) ($p = 0.566$). In the highly social environment of the classroom, inattention in some children – boys and girls - may reflect a specific deficit in attention to social stimuli.

Further investigation of the neuropsychological differences among these groups – children with ASD and ADHD, and girls and boys within each diagnostic category - is needed to determine whether different types of processing deficits underlie inattention in each. For example, it may be that for children with ASD the difficulty is with directing attention to stimuli that are novel or changeable – which includes people, whereas for children with ADHD the difficulty is with sustaining attention to stimuli that are familiar or unchanging. The association between ADHD and the use of pitocin in labor among girls is a novel finding that, if replicated, would have important implications.

Limitations of the current study include the lack of randomized selection of subjects, who represent a narrow range of both socioeconomic background and symptom severity, and therefore these findings may not extend to the general population. Also, while the information regarding birth history provided by parents was judged to be highly reliable, medical records were not examined and the precise amount of pitocin used in each case is unknown, as are other

factors, such as length of labor, indications of fetal distress, and use of analgesic medications, which could differ among diagnostic groups and could influence brain development.

It is clear that perinatal exposure to exogenous OT can disrupt the development of the neural systems of both OT and AVP, with life-long consequences for social emotional functioning. OT and AVP seem to function to balance the opposing needs of the individual both to explore the unknown and to be wary of it, to affiliate with conspecifics and to fight or compete with them. Involvement of both neuropeptides is consistent with the joint deficit in social interaction and novelty seeking that is specific to ASD, and sex differences in their influence on social emotional processes may help explain the strong male bias in ASD, differences in the characteristics of ASD in girls and boys, and the mechanism by which the use of pitocin in labor increases the risk for ASD in boys and ADHD in girls.

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