Altered oxytocin and vasopressin levels in autistic children in Central Saudi Arabia

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ABSTRACT

Objectives: The aim of the current study is to assess plasma levels of oxytocin and vasopressin in autistic children. Also, to correlate plasma levels of those neuropeptides to the degree of autism and age of the affected child. An additional aim is to investigate the role of Pitocin induction in the genesis of autism.

Methods: The study was conducted in Riyadh, Kingdom of Saudi Arabia between September 2003 and April 2004. Seventy-seven autistic child from Riyadh area participated in the study, with the confirmed diagnosis according to DSM-IV diagnostic criteria of autism. The parents/guardians filled a simple related questionnaire, then plasma oxytocin and vasopressin levels were measured in autistic and control children.

Results: Results showed a statistically significant lower plasma level of oxytocin and vasopressin in autistic children as compared to controls. There was no significant correlation between the degree of autism, or the age of the affected child and plasma levels of oxytocin or vasopressin. There was a higher incidence of Pitocin-induced labor among autistics as compared to normal.

Conclusion: Data in this study prove that oxytocin and vasopressin plasma levels were reduced in autistic children which, might be related to abnormal social behavior in autistic children. Higher rates of Pitocin induction were found among the autistic group. The data supports an association between exogenous exposure to oxytocin and neurodevelopmental abnormalities. Further clinical studies are recommended to explore the possible therapeutic effects of oxytocin and vasopressin in autism.

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Both oxytocin and vasopressin are 9-amino acid peptides synthesized in the hypothalamus, and are released into the blood stream through axon terminals in the posterior pituitary or the neurohypophysis. The 2 peptides are closely related, but different in only 2 amino acids.[1] Significant evidence suggests that oxytocin and vasopressin are involved in the regulation of many social behaviors,[2] such as, maternal behavior, infant separation distress and sexual behavior.[3] Animal models lacking the ability to synthesize oxytocin have demonstrated behavioral changes related to emotions and aggression.[4] Based on the fact that social impairment in autism is the main symptom,[5] it has been suggested that the central oxytocin system might be dysfunctional in this population.[6,7] Alterations in oxytocin prohormone processing have been noted as a normal process in development studies in rats and sheep which, showed that processing of the prohormone oxytocin extended form (OT-X) to oxytocin occurs more completely as the fetus matures.[8,9] Research has shown that a group of 30 autistic children had measurably lower plasma levels of oxytocin compared with 30 normal age-matched controls.[6] The relationship between oxytocin levels and child's age and time of day appear to be more tightly regulated in normal children, and correlations between oxytocin and

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cognitive skills and social behaviors are quite different for normal and autistic children. Most importantly, this study found that social impairments were significantly associated with lower oxytocin levels in severely affected (aloof) autistic children, but not in high functioning (active-but-odd) autistic children. Vasopressin, which is structurally very similar to oxytocin, also modulates social behaviors. Vasopressin stimulates social behaviors in birds, frogs and hamsters, stimulates aggression in hamsters, and increases affilative and paternal behavior in voles.[10] In many species, vasopressin is sexually dimorphic, with males having higher levels within the brains than females.[11]

Pitocin the synthetic form of oxytocin is used routinely to accelerate labor and delivery. In the routine use of oxytocin in humans, it is assumed that maternal oxytocin does not cross the placental barrier in amounts sufficient to influence the developing fetus.[12] Despite the widespread use of oxytocin in labor, there are very few studies on the effect of oxytocin on child development. It has been proposed that exposure to Pitocin induction during labor induces down regulation of oxytocin receptors in the developing brain and consequently disturbs the oxytocin system.[13,14] The aim of the current study is to assess plasma levels of oxytocin and vasopressin in autistic children in the Riyadh area, Kingdom of Saudi Arabia. In addition, to correlate plasma levels of these 2 neuropeptides to the degree of autism and age of the affected child. An additional aim is to investigate the role of Pitocin induction in the genesis of autism.

Methods. ***Patient selection.*** The study was conducted in the Riyadh area of the Kingdom of Saudi Arabia (KSA) between September 2003 and April 2004. Seventy-seven children with an age ranging from 3.5-14 years and with a confirmed professional diagnoses of one of the following disorders were selected: early childhood autism, autism, pervasive developmental disorder (PDD), attention deficit disorder (ADD), fragile X syndrome, Rett syndrome, and Asperger syndrome. The diagnosis was carried out either by a qualified psychologist, psychiatrist or neurologist, according to diagnostic criteria DSM-IV. A written consent was obtained from parents prior to the start of the study, and then the parents were asked to fill a questionnaire regarding the child's medical and behavioral history.

Control selection. Seventy-seven healthy age and sex matched controls, were recruited from King Abdul-Aziz University Hospital, Riyadh, KSA.

Biochemical laboratory investigations. Blood samples were collected in EDTA tubes, centrifuged, and plasma was collected and stored at -80°C until assay time. Vasopressin and oxytocin were measured by commercially available ELISA Kits (Phoenix Peptide Pharmaceutical, USA). The tests were carried out in duplicate.

Statistical analysis. The results were analyzed by using the SPSS program for windows. Results were expressed as mean ± SEM. Statistical analysis for differences among the groups was assessed by Student's t-test. A p value of ≤ 0.05 was considered significant. The Spearman test for correlation was used.

Results. Seventy-seven children participated in the study, 71 males (92.2%) and 6 females (7.8%) with a male to female ratio of 11.8 to 1. Sixty-five autistic children (61 males and 4 females) had confirmed diagnosis as follows: 8 males with ADD, 2 males with Asperger syndrome, and 2 female with Rett's syndrome. The mean age for the total number of autistic children participated in the study was 8.8±0.5 years. Type of labor and mode of delivery in the autistic and control groups are shown in **Table 1.** Labor was induced in 41.5% of autistic children as compared to 31.1% in the control group, which is a significant difference ($p<0.05$). Alternately, mode of delivery was approximately similar in both the autistic and control group. Oxytocin plasma concentration was significantly lower in the autistic group (0.074±0.01 ng/ml, $p<0.05$), as compared to the control group (0.107±0.01 ng/ml, $p<0.05$). Further more, vasopressin plasma level was significantly lower in autistic children (0.81±0.03 ng/ml, $p<0.05$) as compared to the control (1.01±0.02). There were no significant correlations between the degree of autism and levels of vasopressin (r=0.2, p=0.13) or oxytocin (r=0.3, p=0.26). Similarly, there were no significant correlations between the age of the affected children and plasma levels of vasopressin (r=0.23, p=0.4), or oxytocin (r=0.15, p=0.23).

Discussion. Results from our study showed that both oxytocin and vasopressin were significantly lower in autistic children as compared to the control.

Table 1 - Comparison of the type of labor and mode of delivery in the autistic and control groups.

Variable	Autistic n (%)	Control n (%)
Type of labor		
Spontaneous	46 (58.5)	53 (68.8)
Induced (Pitocin)	31 (41.5)	24 (31.1)
Total Number	77 (100)	77 (100)
Type of delivery		
Forceps/vacuum	2 (2.5)	2 (2.5)
Cesarian section	16 (20.7)	18 (23)
Normal	59 (76.6)	57 (74)

The levels of both oxytocin and vasopressin were not related to the degree of autism or to the age of the affected child. Results from our study are consistent with that of Modhale et al.[2] The male to female ratio was 11.8 to 1, more than the known international ratio of 4 to 1. This is probably due to more males participating in the study than females. Furthermore, there were higher rates of induced labor among autistic children as compared to controls.

Both cellular and molecular studies have begun to reveal the mechanisms by which oxytocin and vasopressin neural pathways are related, leading to a preliminary understanding of how these hormones act within the brain to influence complex social behaviors. These hormones have unique effects on social behavior, communication and rituals.[15] Some researchers have suggested that oxytocin may play a role in the symptoms of autistic disorder;[2] they reported low plasma oxytocin levels in autistic compared to age matched normal subjects.

Whether abnormalities in oxytocin or vasopressin neurotransmission account for several features of autism need further investigations. These 2 hormones have been implicated in the regulation of behavior in animals, but have not yet been examined in depth in autistic subjects. As autism appears to be a genetic disorder, mutations in peptide receptors or linkage-specific developmental genes could lead to altered oxytocin or vasopressin neurotransmission.[16,17] A profound impairment in social recognition in vasopressin receptors knockout mice has been shown, indicating an important role played by this peptide in social and affective disorders including autism and anxiety disorders.[18] Brain biochemistry seems to be altered, as demonstrated by Young and his group.[19] In a study of 30 controls and 29 autistic children, it was shown that their blood contained on average significantly less oxytocin. They created knockout mice that lacked oxytocin. The animals behaved normally, except they could not learn to recognize other mice or recognize their mother's smell, though their sense of smell was normal. A single dose of oxytocin into the brain, however, cured the mice. With regards to this Young quoted "That gives you hope that if autism is related to oxytocin, it's not permanent".[19]

The hormone, oxytocin, released most commonly during sex and childbirth, is involved in the feeling of caring and warmth sparked off by all sorts of interactions. Varying levels of oxytocin are released for every loving touch or positive feeling for another human being, whether it involves exchanging smiles with a stranger, sharing food, hugging one's kids or even one's dog. Oxytocin does not work alone but is released alongside another prolactin to create bonding between mother and child. The discovery may enable medical scientists to better understand the conditions, which lead some people to suffer from social developmental disorders such as autism, suicidal tendencies, self-abuse, drug addiction and even workaholics.[20,21] There is an argument that Pitocin may cause some cases of autism as so many mothers of autistic children had Pitocin to induce labor. It has been proposed that exposure to high levels of exogenous oxytocin at birth, via Pitocin induction of delivery, might increase susceptibility to autism by causing a down regulation of oxytocin receptors in the developing brain in genetically susceptible children. Gale et al[13] examined the rates of labor induction using Pitocin in children with autism and matched controls with either typical development or mental retardation. Birth histories of 41 boys meeting the criteria for autistic disorder were compared to 25 age- and IQ-matched boys without autism (15 typically developing and 10 with mental retardation). There were no differences in Pitocin induction rates as a function of either diagnostic group (autism versus control) or IQ level (average versus sub average range), failing to support an association between exogenous exposure to oxytocin and neurodevelopmental abnormalities. Others have suggested that the association was more likely caused by the mother/child unit having sulfation problems, which made it difficult for the mother's oxytocin to be produced in sufficient quantity to move labor along, necessitating a jump-start with exogenous oxytocin (Pitocin). The theory is that mothers with sulfation problems would have a higher likelihood for delayed labor.

Results from the current study demonstrated significant lower levels of oxytocin and vasopressin in autistic as compared to normal children, which might be related to abnormal social behavior in autistic children. Further more, results showed a higher incidence of Pitocin induced labor as compared to the normal group. The data supports an association between exogenous exposure to oxytocin and neurodevelopmental abnormalities. Pointing out that it is either that Pitocin induction might induce down regulation of oxytocin receptors in the child’s developing brain, or that the mother has the tendency to secrete less oxytocin, requiring some assistant through Pitocin induction. The child inherits this tendency for low oxytocin levels in the body, as reflected most obviously in his/her behavior. Further clinical studies are recommended to explore the possible therapeutic effects of oxytocin and vasopressin in autism.

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Dedication

This work is dedicated to my colleague the late Dr. Ahmad Al-Jarallah (Consultant Neuropediatrician, King Khaled University Hospital, Riyadh), who gave me all the support I needed when conducting my research on Autism, but did not live to see it completed. "May Allah grant him Jannah (Amen)."

From the Editors: The Editors and Staff of Neurosciences extend their heartfelt condolences to the family, friends and colleagues of Dr. Ahmad Al-JarAllah, a distinguished and respected member of the Neurosciences Community.