CSF and plasma oxytocin levels in suicide attempters, the role of childhood trauma and revictimization

Andreas Chatzittofis [1], **Peter Nordström** [1], **Kerstin Uvnäs-Moberg** [2], **Marie Åsberg** [3], **Jussi Jokinen** [1]

1 The Department of Clinical Neuroscience/Psychiatry, Karolinska Institutet, Karolinska University Hospital, Solna, SE-171 76 Stockholm, Sweden
2 Department of Animal Environment and Health, Swedish University of Agriculture, Skara, Sweden
3 Department of Clinical Sciences, Karolinska Institutet, Danderyd Hospital, Stockholm, Sweden

Correspondence to: Jussi Jokinen
Department of Clinical Neuroscience/Psychiatry
Karolinska Institutet, Karolinska University Hospital/Solna
SE-171 76 Stockholm, Sweden.
TEL: +46-8-51776759; FAX: +46-8-303706; E-MAIL: jussi.jokinen@ki.se

Abstract

OBJECTIVE: Some studies have reported an inverse relationship between childhood adversity and oxytocin levels. The purpose of this study was to assess the relationship between CSF and plasma oxytocin levels and lifetime trauma history in suicide attempters. We hypothesised lower CSF and plasma oxytocin levels in suicide attempters with high exposure to interpersonal violence and negative childhood emotional climate.
METHODS: 28 medication free suicide attempters participated in the study. CSF and plasma morning basal levels of oxytocin were assessed with specific radio-immunoassays. The Karolinska Interpersonal Violence Scale (KIVS) was used to elicit lifetime trauma history and revictimization status and the childhood emotional climate factor was derived from the socialization subscale of the Karolinska Scales of Personality.
RESULTS: Correlations between exposure to interpersonal violence as a child and as an adult and CSF and plasma oxytocin levels were not significant. Revictimized suicide attempters had significantly lower plasma oxytocin levels and more negative childhood emotional climate compared to non-revictimized suicide attempters.
CONCLUSIONS: Our results indicate a complex relationship between life time trauma and the oxytocin system.

INTRODUCTION

Exposure to traumatic events increases risk for physical and mental health problems across a lifespan and child maltreatment is particularly associated with increased risk for adult psychopathology (Teicher & Samson 2013). A disruption of the normal attachment process due to childhood adversity leads to vulnerability to psychiatric disorders and suicidal behaviour (Brodsky & Stanley 2008; Jokinen *et al.* 2010). Furthermore, childhood adversity in form of sexual and physical abuse as well as neglect increases risk for adult revictimization (Widom *et al.* 2008).

Andreas Chatzittofis, Peter Nordström, Kerstin Uvnäs-Moberg, Marie Åsberg, Jussi Jokinen

Oxytocin modulates a variety of behaviours, implicated in learning, memory, affiliation and has an important role in early attachment, social interaction and posttrauma resilience (Heinrichs *et al.* 2009; Neumann 2009; Insel 2010; Olff 2012).

Some human studies have found an inverse relationship between childhood adversity and oxytocin levels. Heim *et al.* (2009) reported lower CSF oxytocin levels in women with a history of childhood abuse compared with women without childhood abuse. Another study showed that early life adverse experience was negatively associated with plasma oxytocin levels in adult healthy men (Opacka-Juffry & Mohiyeddini 2012). Bertsch *et al.* reported a negative correlation between childhood trauma and plasma oxytocin in women with borderline personality disorder (Bertsch *et al.* 2013). Some studies have reported comparatively higher oxytocin levels in relation to childhood trauma: abused women had higher baseline oxytocin in a study using experimental psychosocial challenge paradigm (Pierrehumbert *et al.* 2010). None of these studies has focused on the relationship between oxytocin and revictimization.

We have earlier reported in a cohort of suicide attempters an association between risk for severe suicide attempts and low CSF and plasma oxytocin levels (Jokinen *et al.* 2012). The aim of this study was to investigate the relationship between CSF and plasma oxytocin levels and exposure to interpersonal violence as a child, as an adult or during both periods in the same cohort of suicide attempters. Furthermore, we assessed the relationship between CSF and plasma oxytocin and childhood emotional climate. We hypothesised lower CSF and plasma oxytocin levels in suicide attempters with high exposure to interpersonal violence.

MATERIAL AND METHODS

Study setting

Patients who were hospitalized after a suicide attempt at the psychiatric wards at the Karolinska University Hospital were proposed to participate in a study of biological and psychological risk factors for suicidal behaviour. The Regional Ethical Review Board in Stockholm, Sweden approved the study protocols (Dnrs: 88–216; 91–96) and the participants gave their written informed consent to the study.

Participants

This study involves 28 suicide attempters (18 men, mean age 44 years, S.D. = 14.6, range 23–65 and 10 women, mean age 41 years, S.D. = 12.3, range 26–66) included between the years 1988–1991. Inclusion criteria were a recent suicide attempt and the age of 18 years or older. Exclusion criteria were schizophrenia spectrum psychosis, intravenous drug abuse, or conditions where informed consent could not be obtained. Suicide attempt was defined as any nonfatal, self-injurious behavior with at least some intent to die. The patients were interviewed using the SCID I research version and SCID II to establish diagnosis according to DSM-III (American Psychiatric Association).

Eighty-six percent of the patients had at least one current Axis I psychiatric diagnosis; 50% of patients with Axis I diagnosis fulfilled criteria for a mood disorder, 12.5% for adjustment disorder and one patient for anxiety disorders, 29% had a substance related disorder (alcohol) and one a personality disorder (organic). Two patients had a co morbid alcohol abuse diagnosis. Among Axis II diagnoses, two thirds of the patients fulfilled criteria for a personality disorder. Patients were medication free at inclusion and at lumbar puncture. The study population has recently been described in detail (Jokinen *et al.* 2012).

CSF and plasma oxytocin assays

Lumbar punctures were performed in a standardized manner between 8 and 9 a.m. after fasting in bed since midnight. 12 mL CSF was withdrawn with the participant in the sitting position, the needle being inserted between lumbar vertebrae IV and V. CSF was immediately centrifuged and aliquoted in six 2 mL samples and stored at –80 °C for pending analysis of oxytocin. Fifteen minutes before lumbar puncture, blood samples (6 mL) were collected in tubes containing heparin (10 IU/mL) and Trasylol (500 IU/mL) and were centrifuged. The plasma was removed and frozen at –80 °C.

The concentration of oxytocin in plasma and CSF was measured with specific radioimmunoassay (RIA) using the antibody KA19 (Milab, Malmo, Sweden). The limit of oxytocin detection was 2 fmol/mL and the intra- and inter-assay coefficients of variation were 11.2% and 13%, respectively (Stock & Uvnäs-Moberg 1985; Uvnäs-Moberg *et al.* 1993).

Assessments

Patients were assessed with The Karolinska Interpersonal Violence Scale (KIVS) concerning childhood and adult trauma. KIVS contains four subscales assessing exposure to violence and expressed violent behavior in childhood (between 6–14 years of age) and during adult life (15 years or older) (Jokinen *et al.* 2010). The items were scored 0–5. Exposure to interpersonal violence as a child and as an adult was used in the analysis. Revictimization was defined as having both ratings above the mean and the sum score 6 or above (Table 1).

Childhood emotional climate was assessed using socialization subscale from the Karolinska Scales of Personality (KSP). The Socialization subscale consists of 20 items, emphasizing negative childhood experiences, poor school and family adjustment, and general dissatisfaction. Eight of the items reflect negative childhood emotional climate, 4 items childhood adjustment problems and 8 items feeling of resentment and victimization (Svanborg *et al.* 1999). Childhood emotional climate factor of the Socialization subscale was used in the analysis.

Data analysis

Initial analyses were carried out to evaluate skewness and kurtosis of the distributions with Shapiro Wilks test. Correlation analyses (Spearmans rho) were used to determine associations between the clinical ratings and oxytocin levels. Group differences were assessed with Wilcoxon test and t-test. Post-hoc power analysis indicated that we were only able to detect large effect sizes. The *p*-value was set at <0.05. The Statistical Package JMP VI software, SAS Institute inc., Cary, NC, USA was used for all statistical analyses.

RESULTS

Clinical ratings of exposure to interpersonal violence

The mean exposure to interpersonal violence as a child was 2.5 (S.D. = 1.6, range 0–5) and the mean exposure to interpersonal violence as an adult was 1.9 (S.D. = 1.6, range 0–5). There was a significant correlation between the exposure to interpersonal violence as a child and exposure as an adult (rho= 0.58, *p*=0.004). Eight suicide attempters (5 women and 3 men, mean age = 42 years) were characterized as revictimized and 15 as non-revictimized (3 women and 12 men, mean age = 43 years). Total lifetime trauma exposure in revictimized suicide attempters (Mean±SD, range) (7.8±1.4, 6–9) was significantly higher compared to non-revictimized suicide attempters (Mean±SD) (2.7±1.5, 0–5) (F-ratio=63.1, *p*<0.0001). Revictimized patients did not score higher in depression severity (MADRS) or fulfilled more often criteria for comorbid personality disorder or substance abuse (*p*-values 0.47–0.84).

Clinical ratings of childhood emotional climate

Childhood emotional climate showed a significant negative correlation with KIVS exposure to interpersonal violence as a child and exposure as an adult ratings (rho=−0.63, *p*=0.005; rho=−0.64, *p*=0.004). Childhood emotional climate scores were significantly lower in revictimized suicide attempters (Mean±SD) (16.1±3.7) compared to non-revictimized suicide attempters (Mean±SD) (22.5±5.7), (*p*=0.02).
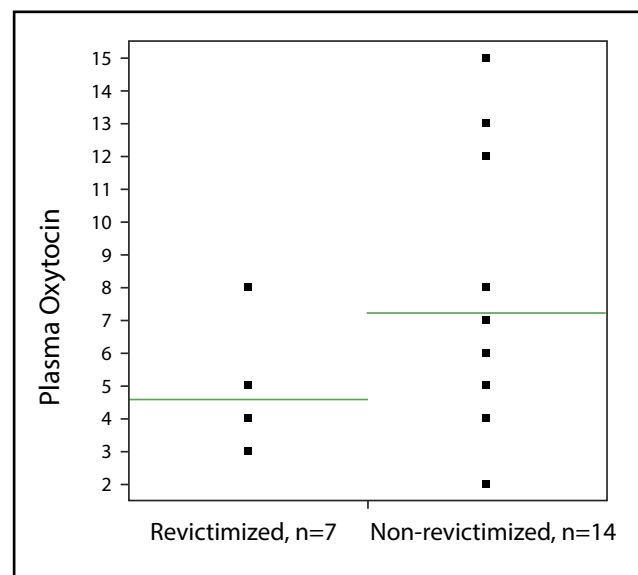
Tab. 1. Definition of revictimization.

The KIVS score	The KIVS statements As a child	The KIVS statements As an adult
0	No violence.	No violence.
1	Occasional slaps. Fights in school, of no great significance.	Threatened or subjected to a low level of violence on at least one occasion.
2	Bullied occasionally for short period(s). Occasionally exposed to corporal punishment.	Beaten by partner on occasion. Victim of purse snatching. Threatened with object.
3	Often bullied. Frequently exposed to corporal punishment. Beaten by drunken parent.	Threatened with a weapon. Robbed. Beaten by someone other than partner. Frequently beaten by partner.
4	Bullied throughout childhood. Battered/ beaten up by schoolmates. Regularly beaten by parent or other adult. Beaten with objects. Sexually abused.	Raped. Battered.
5	Repeated exposure to violence at home or in school that resulted at least once in serious bodily harm. Repeated sexual abuse, or sexual abuse that resulted in bodily harm.	Repeatedly raped. Repeatedly battered. Severely battered, resulting in serious bodily harm.

Fig. 1. Mean plasma oxytocin levels in revictimized and non-revictimized suicide attempters.

Tab. 2. CSF and plasma Oxytocin levels (fmol/mL) in revictimized and non-revictimized suicide attempters. Univariate test method, Wilcoxon test.

Endocrine measure	Non-revictimized Suicide attempters				Revictimized Suicide attempters				Statistics
	Mean	Median	SD	Range	Mean	Median	SD	Range	*p*-value
CSF Oxytocin N=13 vs 8	10.9	11	3	7-17	11	10.5	4	6-19	*p*=0.85
Plasma Oxytocin N=14 vs 7	7.2	6	3.7	2-15	4.6	4	1.7	3-8	*p*=0.046

CSF and plasma Oxytocin levels, exposure to interpersonal violence and childhood emotional climate

The correlations between CSF or plasma oxytocin and exposure scores to interpersonal violence as a child and as an adult were not significant (rho=0.16, p=0.49; rho=0.04, p=0.85), (rho=−0.23, p=0.31; rho=−0.30, p=0.18). Revictimized suicide attempters had significantly lower plasma oxytocin levels compared to non-revictimized suicide attempters (p=0.046) whereas the CSF oxytocin levels did not differ significantly between the two groups (p=0.85), Table 2. Figure 1 shows mean plasma oxytocin levels in revictimized and non-revictimized suicide attempters.

The correlations between CSF or plasma oxytocin and childhood emotional climate were non-significant (p=0.35, p=0.78).

DISCUSSION

In the present study, the correlations between exposure to interpersonal violence as a child and as an adult and CSF and plasma oxytocin levels were not significant. Interestingly, revictimized suicide attempters had lower plasma oxytocin levels compared to non-revictimized suicide attempters. To our knowledge this is the first time this relationship is reported. The lack of significant association between oxytocin and childhood trauma is in contrast with some previous studies reporting negative correlations between CSF and plasma oxytocin levels and childhood trauma (Heim *et al.* 2009; Bertsch *et al.* 2013; Opacka-Juffry & Mohiyeddini 2012). However, due to the small sample size, we were able to detect only large effects of childhood trauma on oxytocin levels, which implies caution when interpreting the negative findings of the study. Furthermore, our sample consisted of suicide attempters with a high burden of psychopathology whereas Heim *et al.* (2009) and Opacka-Juffry and Mohiyeddini (2012) investigated volunteers. In addition, different instruments were used in the evaluation of childhood trauma, KIVS does not measure separately neglect and emotional abuse, and the earlier studies have reported a particularly strong effect for neglect and emotional abuse. We used a measure for childhood emotional climate which was strongly correlated with KIVS exposure ratings indicating that risk for exposure to interpersonal violence as a child may be higher in families with negative emotional climate and that there is a considerable accumulation of different types of childhood adversity.

As expected, we found a significant correlation between the exposure to interpersonal violence as a child and exposure as an adult which is in line with the literature of lifetime revictimization (Widom *et al.* 2008). Across different types of traumas and experiences of victimization, abused and neglected children are at increased risk of revictimization later in life and victims of multiple forms of abuse or neglect usually

evince highest risk of revictimization (Widom *et al.* 2008). In our cohort of suicide attempters, the level of exposure to interpersonal violence as a child was high and more than one third of the patients were revictimized. The revictimized suicide attempters had lower childhood emotional climate scores compared to non revictimized suicide attempters but they were not more depressed nor had more psychiatric comorbidity. Thus, revictimization seems to be related more to childhood experiences than the current state.

One possible explanation for lower plasma oxytocin levels in the revictimized group might be that they may have a more profound dysfunction in the oxytocin system and that this dysfunction can contribute to the process of revictimization as earlier proposed (Heim *et al.* 2009). Another explanation would be that the oxytocin dysfunction is indirectly related to childhood trauma (Bertsch *et al.* 2013).

CSF and plasma oxytocin levels were measured with specific radio-immunoassay. The levels obtained were equivalent to those obtained in other clinical studies (Heim *et al.* 2009). As the levels of oxytocin in the suicide attempters was low, it is possible that a small decrease in oxytocin levels in individuals having experienced trauma in childhood or adulthood alone could not be detected for methodological reasons whereas it was possible to detect the more profound decrease in the revictimized subjects.

The strength of the study was the assessment of exposure to interpersonal violence both in childhood and in adulthood with the same structured clinical interview which makes it possible to assess the revictimization status. Oxytocin was assessed both in plasma and in CSF. This study is a second post-hoc analysis of oxytocin data in a cohort of suicide attempters (Jokinen *et al.* 2012). We have earlier published an association between low CSF oxytocin levels in suicide attempters with high suicide intent (Jokinen *et al.* 2012). Among the limitations of this study, is the cross-sectional study design, which prevents us from drawing casual conclusions. Some other limitations of the study should also to be pointed out, particularly the small sample size, which jeopardizes the interpretation of negative findings, since we were able to detect only large effect sizes. We had also some missing data and we did not have an appropriate matched healthy control group. We did not either have the information of menstrual cycle and possible use of hormonal preparations. Furthermore, childhood trauma was assessed retrospectively with only one clinical instrument. A complementary assessment with the Childhood Trauma Questionnaire measuring even emotional neglect would have strengthened the study design.

CONCLUSION

We assessed the relationship between CSF and plasma oxytocin levels and lifetime trauma history in suicide attempters. Revictimized suicide attempters had

lower plasma oxytocin and more negative childhood emotional climate indicating a complex relationship between life time trauma and the oxytocin system.

ACKNOWLEDGEMENTS

REFERENCES

1 Bertsch K, Schmidinger I, Neumann ID, Herpertz SC (2012). Reduced plasma oxytocin levels in female patients with borderline personality disorder. Horm. Behav. **63**: 424–429.
2 Brodsky BS, Stanley B (2008). Adverse Childhood Experiences and Suicidal Behavior. Psychiatr. Clin. North Am. **31**: 223–235.
3 Heim C, Young LJ, Newport DJ, Mletzko T, Miller AH, Nemeroff CB (2009). Lower CSF oxytocin concentrations in women with a history of childhood abuse. Mol. Psychiatry. **14**: 954– 958.
4 Heinrichs M, von Dawans B, Domes G (2009). Oxytocin, vasopressin, and human social behavior. Front. Neuroendocrinol. **30**: 548–557.
5 Insel TR (2010). The Challenge of Translation in Social Neuroscience: A Review of Oxytocin, Vasopressin, and Affiliative Behavior. Neuron. **65**: 768–779.
6 Jokinen J, Chatzittofis A, Hellström C, Nordström P, Uvnäs-Moberg K, Åsberg M (2012). Low CSF oxytocin reflects high intent in suicide attempters. Psychoneuroendocrinology. **37**: 482–490.
7 Jokinen J, Forslund K, Ahnemark E, Gustavsson P, Nordström P, Åsberg, M (2010). Karolinska Interpersonal Violence Scale predicts suicide in suicide attempters. J. Clin. Psychiatry. **71**: 1025–1032.
8 Neumann ID (2009). The advantage of social living: brain neuropeptides mediate the beneficial consequences of sex and motherhood. Front. Neuroendocrinol. **4**: 483–496.
9 Olff M (2012). Bonding after trauma: On the role of social support and the oxytocin system in traumatic stress. Eur. J. Psychotraumatol. **3**: 18597-http://dx.doi.org/10.3402/ejpt.v3i0.18597.
10 Opacka-Juffry J, Mohiyeddini C (2012). Experience of stress in childhood negatively correlates with plasma oxytocin concentration in adult men. Stress. **15**: 1–10.
11 Pierrehumbert P, Torrishi R, Laufer D, Halfon O, Ansermet F, Beck Popovic M (2010). Oxytocin response to an experimental psychosocial challenge in adults exposed to traumatic experiences during childhood or adolescence. Neuroscience. **166**: 168–177.
12 Stock S, Uvnäs-Moberg K (1985). Oxytocin infusions increase plasma levels of insulin and VIP but not of gastrin in conscious dogs. Acta Physiol. Scand. **125**: 205–210.
13 Svanborg P, Gustavsson PJ, Mattila-Evenden M, Asberg M (1999). Assessment of maladaptiveness: a core issue in the diagnosing of personality disorders. J. Pers. Disord. **13**: 241–56.
14 Teicher MH, Samson JA (2013). Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. Am. J. Psychiatry. **170**: 1114–33.
15 Uvnäs-Moberg K, Bruzelius G, Alster P, Lundeberg T (1993). The antinociceptive effect of non-noxious sensory stimulation is mediated partly through oxytocinergic mechanisms. Acta Physiol. Scand. **149**: 199–204.
16 Widom CS, Czaja SJ, Dutton MA (2008). Childhood victimization and lifetime revictimization. Child Abuse Negl. **32**: 785–796.