Social Support and Oxytocin Interact to Suppress Cortisol and Subjective Responses to Psychosocial Stress

Markus Heinrichs, Thomas Baumgartner, Clemens Kirschbaum, and Ulrike Ehlert

Background: The presence of social support has been associated with decreased stress responsiveness. Recent animal studies suggest that the neuropeptide oxytocin is implicated both in prosocial behavior and in the central nervous control of neuroendocrine responses to stress. This study was designed to determine the effects of social support and oxytocin on cortisol, mood, and anxiety responses to psychosocial stress in humans.

Methods: In a placebo-controlled, double-blind study, 37 healthy men were exposed to the Trier Social Stress Test. All participants were randomly assigned to receive intranasal oxytocin (24 IU) or placebo 50 min before stress, and either social support from their best friend during the preparation period or no social support.

Results: Salivary free cortisol levels were suppressed by social support in response to stress. Comparisons of pre- and poststress anxiety levels revealed an anxiolytic effect of oxytocin. More importantly, the combination of oxytocin and social support exhibited the lowest cortisol concentrations as well as increased calmness and decreased anxiety during stress.

Conclusions: Oxytocin seems to enhance the buffering effect of social support on stress responsiveness. These results concur with data from animal research suggesting an important role of oxytocin as an underlying biological mechanism for stress-protective effects of positive social interactions. Biol Psychiatry 2003;54:1389–1398 © 2003 Society of Biological Psychiatry

Key Words: Social support, oxytocin, stress, cortisol, anxiety, intranasal

Introduction

There is substantial evidence indicating that psychosocial risk factors (e.g., lack of social contact, death of a spouse) contribute to a wide spectrum of somatic, psychosomatic, and psychiatric disorders with major public health significance, such as depression or coronary heart disease (Bruce 2002; Ehlert and Straub 1998; Kraemer et al 2001; Rozanski et al 1999; Ruberman et al 1984; Smith and Ruiz 2002). Positive social interactions have in turn been shown to exert powerful beneficial effects on health outcomes and longevity. Social support is the most intensively investigated social factor in humans (Broadhead et al 1983; House et al 1988; Knox and Uvnas-Moberg 1998; MacMahon and Lip 2002; Paykel 2001; Schwarzer and Leppin 1991; Seeman 2000; Seeman and McEwen 1996; Uchino et al 1996; Veiel and Baumann 1992). A growing body of research in clinical populations has provided support for the hypothesis that higher reported levels of social support are associated with positive effects on various diseases, such as cardiovascular reactivity and blood pressure (Evans and Steptoe 2001; Gallo et al 2000; Spitzer et al 1992; Steptoe 2000; Uchino et al 1999; Uno et al 2002), depression (Hays et al 2001; Sayal et al 2002), and schizophrenia (Buchanan 1995; Erickson et al 1998; Macdonald et al 1998). In addition, physiologic stress reactivity in experimental studies has also been shown to be responsive to social support. The availability of social support has been associated with attenuated free cortisol concentrations in saliva (Kirschbaum et al 1995) and lower cardiovascular reactivity (Gerin et al 1992; Lepore et al 1993; Uchino and Garvey 1997) in response to acute laboratory stress.

Although there is considerable knowledge concerning the positive effects of social support on morbidity and mortality risks, to date, less attention has been given to the underlying physiologic mechanisms or pathways. More specifically, it is not clear how positive social interactions suppress stress-responsive physiologic systems or stimulate other internal regulatory systems involved in the attenuation of stress reactivity. A better understanding of these mechanisms would undoubtedly have important
clinical implications for differential diagnosis and specific psychological and pharmacologic treatments for numerous disorders.

In animals, the neuropeptide oxytocin has been shown to exert behavioral and physiologic stress-attenuating and anxiolytic effects and, in addition, might prove to promote positive social interaction (Carter 1998; Carter and Altemus 1997; Legros 2001; McCarthy and Altemus 1997; Pedersen 1997; Pedersen and Boccia 2002; Uvnas-Moberg 1998). Oxytocin is synthesized in magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus (Swaab et al 1975; Vandesande and Dierickx 1975). It is processed from its precursor form, together with the carrier protein, along the axonal projection to the posterior pituitary, from which the peptide is secreted into the systemic circulation (Brownstein et al 1980). In addition, oxytocin is widely distributed throughout the central nervous system from smaller parvocellular neurons, influencing many neurobehavioral functions (de Wied et al 1993; McCarthy and Altemus 1997). In experimental studies in animals, oxytocin has been stimulated both exogenous (e.g., intracerebroventricular injection) and endogenous (e.g., suckling stimulus during lactation) methods of stimulation. Aside from the most well-known peripheral role of oxytocin in parturition and lactation, intracerebral oxytocin inhibits the stress-induced activity of the hypothalamic–pituitary–adrenal (HPA) axis responsiveness, suggesting an inhibitory influence of oxytocin on stress-responsive neurohormonal systems (Neumann et al 2000a, 2000b; Uvnas-Moberg et al 1994, 1999; Windle et al 1997b). Moreover, the neuropeptide has been shown to function as a central regulator in social attachment and in related prosocial behaviors (Carter 1998; Insel 1997; Insel and Young 2001; Pedersen 1997).

In contrast to the very active investigation in recent years into the effects of oxytocin on physiologic and behavioral stress and anxiety responses in animals, research in humans remains relatively limited; however, initial studies suggest similar stress-reducing effects of the neuropeptide in humans. Similar to the aforementioned studies in lactating rodents, the lactation paradigm for endogenous stimulation has also been used in human studies. In lactating women, a suppression of endocrine stress responses has been observed if breast-feeding starts 30–60 min before stress exposure, depending on the kind of stressor (Altemus et al 1995, 2001; Heinrichs et al 2001, 2002). Within this context, however, it should be noted that there are a variety of confounding factors, in particular the release of other hormones, that are difficult to control for in endogenous stimulation paradigms. Thus, the specific effects of central oxytocin as an underlying biological mechanism for the reduction of stress and anxiety and for positive social interactions in humans are yet to be determined. Alternatively, studies on central effects of oxytocin and vasopressin in healthy humans and patients have been carried out with exogenous stimulation with intranasal administration (Born et al 1998; Bruins et al 1992; Heinrichs 2000; Pitman et al 1993). Neuropeptides have recently been shown to enter the cerebrospinal fluid directly after intranasal administration (Born et al 2002). To date, there have been no human studies that directly address effects of oxytocin administration and social support on stress and anxiety. With these considerations in mind, we set out to study the effects of oxytocin and social support on mood, anxiety, and neuroendocrine responses to psychosocial stress (public speaking and mental arithmetic in front of an audience) in healthy men.

Methods and Materials

Participants

Thirty-seven healthy men (mean ± SD age, 23.8 ± 3 years) were recruited by advertisements posted at the university and were paid for participation. The study was conducted at the University of Trier, Germany. All subjects underwent a physical evaluation to screen out chronic diseases, mental disorders, medication, smoking, and drug or alcohol abuse. Participants abstained from food and drink (other than water) for 2 hours before the experiment, and from exercise, caffeine, and alcohol during the 24 hours before the session. Three of the original 40 subjects were excluded: one who scored at 65 (the 100th percentile) in the State-Trait-Anxiety Inventory (Laux et al 1981) and two who were found to have taken medication because of acute seasonal allergic rhinitis. The study was carried out in accordance with the Declaration of Helsinki principles and approved by the institutional ethics committee. All subjects gave written, informed consent and were informed of their right to discontinue participation at any time.

Social Support Provision

Two weeks before the experiment, subjects were randomly instructed in writing either to bring their best friend (male or female) along with them to the experimental session ("social support") or to come alone ("no social support"). Support providers were told that their task during the experiment was to be as helpful as possible during the 10-min preparation for the speech task (see Stress Procedure) and offer both instrumental and emotional support. More specifically, they were told that they would know best what kind of supportive behaviors would fit the individual coping preferences of the subject. Support providers were present only during preparation of the stressor.

Oxytocin Administration

Participants received a single dose of 24 IU oxytocin (Syntocinon-Spray, Novartis, Basel, Switzerland) intranasally or placebo. Intranasal administration took place immediately after the introduction at the beginning of the experiment (50 min before stress exposure); a dose of 12 IU was sprayed into each nostril (three
Salivary Cortisol Measures

Salivary cortisol is considered a reliable and valid measure of unbound ("free") cortisol concentrations in plasma (Vining and McGinley 1987). A commercially available sampling device (Salivet; Sarstedt, Rommelsdorf, Germany) was used to obtain eight saliva samples from each participant over the course of the stress session. Saliva samples were collected before the preparation phase (baseline: −20 min relative to TSST) and immediately before stress (prettrial: −1 min). Six additional samples were collected during the 60-min poststress period (+1, +10, +20, +30, +45, and +60 min).

After being chewed for about 60 sec, devices were stored at −20°C until required for biochemical analysis. Before assaying for cortisol, samples were thawed and spun at 3000 rpm for 5 min to obtain 5–1.0 mL clear saliva with low viscosity. The free cortisol concentration in saliva was analyzed with a time-resolved immunoassay with fluorescence detection, as described previously (Dressendorfer et al. 1992). The limit of detection was .5 nmol/L for saliva cortisol. Inter- and intra-assay coefficients of variance were below 12% and 10%, respectively.

Psychological Measures

Depression and anxiety were assessed by the German versions of the Self-Rating Depression Scale (Zung 1965) and the State-Trait Anxiety Inventory (Laux et al. 1981). To assess the general availability of social support, we used the German version of the Interpersonal Support Evaluation List (Laireiter 1996). This questionnaire measures the perceived availability of social support resources. We used a mood questionnaire that is especially suited for repeated measures within several minutes or hours (Steyer et al. 1997). Twelve items are rated on a 5-point scale, ranking from 1 ("not at all") to 5 ("very strongly"). Factor analysis revealed three scales, termed elevated versus depressed mood, wakefulness versus sleepiness, and calmness versus restlessness. Self-reported affect was assessed by measuring mood and state anxiety before and after stress exposure.

Data Analyses

For each variable of interest, we used three-way analyses of variance (ANOVA) with repeated measurement (social support × oxytocin × time [repeated factors: eight for cortisol and two for anxiety and mood, respectively]) (Winer 1971). When the Mauchly test of sphericity indicated heterogeneity of covariance, we verified repeated-measures results with Greenhouse-Geisser corrections. To determine where significant differences from baseline hormone levels in groups were occurring, multiple single comparisons were conducted with an adjusted level of significance (t test with Bonferroni corrections). The areas under the individual response curves were calculated with the trapezoid formula, aggregating the eight saliva hormone levels during the stress protocol. Statistical tests were two-tailed and conducted at the .05 level of significance.

Results

Description of the Study Groups

As described in Methods and Materials, all participants were randomly assigned to receive intranasal oxytocin (24 IU) or placebo 50 min before stress, and either no social support or social support from their best friend during the
10-min preparation period (placebo-controlled, double-blind, 2 × 2 factorial design). As shown in Table 1, subjects of the four study groups did not differ significantly with respect to age and body mass index. There were no differences in the perceived availability of general social support among groups. Trait anxiety (36.5 ± 1.0) and depression scores (40.6 ± 1.1) of all participants were within the normal range for the general population.

Cortisol Responses to Stress

In the overall analyses, three-way analysis of variance with repeated measurement revealed the expected significant salivary free cortisol response to stress in the total group [time effect: \( F(2.4,80.5) = 37.40, p < .001 \)]. Figure 1 depicts the means and standard errors among groups for saliva cortisol at each time point and the area under the response curves. No significant differences in pretrial cortisol levels were observed among groups 1 min before stress. There was a significant attenuating effect of social support [social support × time effect, \( F(2.4,80.5) = 8.52, p < .001 \)] and a trend toward attenuated cortisol levels by oxytocin [oxytocin × time effect, \( F(2.4,80.5) = 2.45, p = .08 \)]. More importantly, a significant three-way interaction effect was obtained [social support × oxytocin × time effect: \( F(2.4,80.5) = 4.54, p < .01 \)], with the lowest cortisol concentrations during stress in subjects who received both social support and oxytocin.

The mean absolute increase in salivary cortisol in response to stress was 15.1 nmol/L in subjects without social support and with placebo, 3.6 nmol/L in subjects with social support and placebo, 6.7 nmol/L in subjects without social support and with oxytocin, and 4.0 nmol/L in subjects with both social support and oxytocin. Subjects without social support and with placebo showed significantly higher cortisol levels at 1, 10, 20, 30, 45, and 60 min after cessation of stress compared with pretrial levels 1 min before stress (all \( p < .05 \) with Bonferroni correction), whereas subjects without social support and with oxytocin yielded significant cortisol increases at 1, 10, and 20 min after stress exposure (all \( p < .05 \) with Bonferroni correction). Notably, no significant cortisol increases after stress in comparison with pretrial concentrations occurred in the group with social support and oxytocin, whereas the other groups showed significant increases.

Table 1. Characteristics of Study Groups

<table>
<thead>
<tr>
<th></th>
<th>No Social Support and Placebo (( n = 8 ))</th>
<th>Social Support and Placebo (( n = 10 ))</th>
<th>No Social Support and Oxytocin (( n = 8 ))</th>
<th>Social Support and Oxytocin (( n = 11 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.0 ± 1.0</td>
<td>23.3 ± .9</td>
<td>22.6 ± 1.0</td>
<td>23.5 ± .9</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>23.6 ± .7</td>
<td>22.4 ± .6</td>
<td>22.2 ± .7</td>
<td>22.3 ± .6</td>
</tr>
<tr>
<td>Social Support (ISEL score)</td>
<td>71.8 ± 4.5</td>
<td>77.0 ± 4.0</td>
<td>70.4 ± 4.5</td>
<td>75.4 ± 3.8</td>
</tr>
</tbody>
</table>

Data given as mean ± SEM. ISEL, Interpersonal Support Evaluation List.
Mood and Anxiety Responses to Stress

Mood and anxiety were assessed before and after the psychosocial stress test. Analysis of variance with repeated measurement revealed a significant three-way interaction effect on calmness [social support × oxytocin × time effect: $F(1,33) = 4.14, p = .05$] (Figure 2). No significant differences in calmness before stress induction were observed among groups. As expected, subjects without social support and with placebo exhibited a decrease in calmness during stress (before: $13.3 \pm 1.4$; after: $11.3 \pm 1.7$). In contrast, participants who received either social support (before: $9.8 \pm .9$; after: $12.8 \pm 1.2$) or oxytocin (before: $12.9 \pm 9$; after: $14.4 \pm .7$) showed increasing calmness during the stress procedure (Figure 2). No changes in the mood and wakefulness scales were observed.

A trend toward a three-way interaction on state anxiety was obtained [social support × oxytocin × time effect: $F(1,33) = 4.05, p = .052$]. Again, there were no significant differences in anxiety scores among groups before stress. The group without social support and with placebo showed the expected increase in anxiety (before: $39.0 \pm 2.9$; after: $41.8 \pm 4.3$), whereas participants with either social support (before: $47.4 \pm 3.0$; after: $43.0 \pm 2.8$) or oxytocin (before: $42.9 \pm 2.6$; after: $38.1 \pm 2.3$) showed decreasing anxiety during stress. Importantly, comparisons of pre- and poststress anxiety levels revealed a significant anxiolytic effect of intranasal oxytocin administration within the group that received oxytocin but not social support [$r(7) = 2.68, p < .05$].

Discussion

This is the first study on the effects of social support and oxytocin on endocrine, mood, and anxiety responses to psychosocial stress in humans. Participants who received both protective factors of social support and oxytocin exhibited the lowest cortisol concentrations during stress exposure, whereas subjects who received no social support and placebo demonstrated the highest cortisol response (Figure 1). Most notably, we found corresponding results in psychological measures, indicating that subjects without social support and with placebo showed the expected decrease in calmness and an increase in anxiety during stress. In contrast, participants who received either social support or oxytocin or both protective factors showed increasing calmness and decreasing anxiety scores during the stress procedure (Figure 2). Moreover, pre- and poststress comparisons of anxiety showed an anxiolytic effect of oxytocin administration. The present data build on prior research by demonstrating effects of social support both at the physiologic and the psychological level of analysis and, in addition, by experimentally varying a possible underlying endocrine mechanism, the neuropeptide oxytocin. It might be concluded that the interaction effect of oxytocin and social support on both endocrine and subjective measures accounts for a central nervous mechanism in humans.

In the present study, we obtained further evidence of blunted physiologic stress responsiveness by social support in men, replicating previous reports on attenuated salivary cortisol levels (Kirschbaum et al 1995) and lower cardiovascular reactivity (Gerin et al 1992; Lepore et al 1993; Uchino and Garvey 1997) in response to a psychosocial stressor. Once again, it is acute available instrument and emotional support offered by another person that is associated with a suppression of stress-responsive physiologic systems (in this case, free cortisol in saliva; Figure 1). Socially supported subjects might appraise the anticipated acute stressor as less threatening and more controllable than unsupported subjects (Kirschbaum et al 1995). These results from laboratory research are in accordance with clinical studies indicating numerous health benefits of social support (Buchanan 1995; Erickson et al 1998; Evans and Steptoe 2001; Gallo et al 2000; Hays et al 2001;
Recently demonstrated attenuated pituitary–adrenal reactivity to psychosocial stress after endogenous stimulation of oxytocin after breast-feeding in postpartum lactating women (Heinrichs et al 2001). In addition, lactating women had reduced plasma ACTH, cortisol, and glucose responses to physical stress in comparison with postpartum nonlactating women (Altemus et al 1995). Breastfeeding mothers with increased plasma oxytocin in response to a speech stressor that immediately followed baby holding had lower blood pressure than did mothers with a decrease in oxytocin after stress (Light et al 2000). Moreover, nonpostpartum healthy women who showed increased plasma oxytocin levels in response to positive emotion and massage as well as maintained oxytocin levels during negative emotion were less likely to report interpersonal problems associated with intrusiveness (Turner et al 1999). Finally, studies on psychiatric disorders show decreased oxytocin concentrations, for example in plasma in patients with autism (Green et al 2001; Modahl et al 1998), in plasma in high-scoring pain and depression in fibromyalgia syndrome patients (Anderberg and Uvnas-Moberg 2000), and in cerebrospinal fluid in patients with anorexia nervosa and bulimia nervosa (Demitrack et al 1990). Interestingly, cerebrospinal fluid oxytocin was normal in subjects after recovery from bulimia nervosa and anorexia nervosa (Frank et al 2000).

In contrast, increased concentrations of oxytocin have been observed in cerebrospinal fluid of patients with Prader-Willi syndrome and obsessive-compulsive disorder (Leckman et al 1994; Martin et al 1998), whereas other studies could not find differences between patients with obsessive-compulsive disorder and healthy control subjects (Altemus et al 1999). Although it is difficult to draw conclusions about oxytocin functioning in specific brain regions from peripheral or cerebrospinal fluid measurement, the data do suggest that dysfunctions of oxytocin metabolism might be related to several psychiatric disorders.

Despite the stress-buffering effect of endogenous stimulation of peripheral oxytocin concentrations, it is difficult to control for the potential impact of confounding factors, especially other hormones, such as prolactin or opioid peptides. By using double-blind, placebo-controlled intranasal administration in our study, we circumvented the difficulties of unspecific stimulation paradigms. Several pathways to the brain have been demonstrated to pass the blood–brain barrier in neuropharmacologic research, and there is convincing evidence that peptides gain access to the brain after intranasal administration, bypassing the bloodstream (e.g., extracellular pathway, intraneuronal transport; Born et al 1998, 2002; Heinrichs 2000). Indeed, studies on intranasal oxytocin administration have been reported showing amnesic effects on memory performance (Bruins et al 1992) and inhibited physiologic responding in posttraumatic stress disorder (Pitman et al 1993), although studies on obsessive-compulsive disorder have revealed no effects of intranasal oxytocin (den Boer and Westenberg 1992; Epperson et al 1996). Overall, a great deal remains to be specified regarding adequate measurement of centrally active oxytocin in humans. Controversy exists, for example, as to the correlation between oxytocin
concentrations in blood and brain (Amico et al. 1990; Engelmann et al. 2000; Neumann et al. 1993; Wotjak et al. 1998). Human studies that include measurement of oxytocin concentrations in cerebrospinal fluid during social interaction and stress exposure are needed to further evaluate the central nervous role of the neuropeptide.

We have hypothesized that social support might attenuate endocrine and subjective responses to psychosocial stress. As known from animal research, this stress-protective effect of social support might be mediated through increased oxytocin concentrations, which were experimentally varied by placebo-controlled, double-blind intranasal administration. Indeed, we found that social support alone attenuated cortisol stress responses to a greater extent than did oxytocin alone. On the other hand, intranasal oxytocin had an anxiolytic effect with regard to pre- and poststress comparisons of anxiety levels; however, both social support and oxytocin together showed the highest stress-protective and anxiolytic effect. In sum, the effectiveness of social support might be connected with a sufficient central nervous availability of oxytocin. We therefore suggest that the peptide hormone might prove to be important in the stress-protective effect of positive social interaction, and, in turn, a dysregulated oxytocin metabolism might be associated with clinical disorders of psychosocial relevance. Future studies should explore whether patients with psychiatric disorders that are associated with social deficits (e.g., social phobia, autism) or patients with stress-related disorders could have characteristic dysfunctions in oxytocin metabolism. Prospective longitudinal data might help to model this potential interaction linking social behavior, oxytocin, and stress responsiveness. Furthermore, more direct investigations of central nervous system oxytocin function, including neuroimaging (e.g., radioactive labeling of the neuropeptide in positron emission tomography), are warranted. Finally, the neuropeptide might be a novel target for neuropsychopharmacologic research.

We thank the study participants and acknowledge the technical contributions and assistance of (in alphabetical order) Jutta Bennecke, Uta Berger, Begga Beyersmann, Ulrike Bucerius, Bernhild Doll, Anuschka Enzler, Annemarie Fritzen, Sarah Mannion, Gunther Meinschmidt, Rita Praprotnik, Ingrid Rummel-Frühau, Katrin Ruwisch, Silke Welter, Cornelia Zenglein, and Britta Zimmermann. The study was conducted at the Center for Psychobiological and Psychosomatic Research, University of Trier, Germany. Our grateful thanks to Professor Dirk H. Hellhammer for his support. We thank Dr. Dominique J. de Quervain for reviewing an early version of the manuscript.

References


Macdonald EM, Jackson HJ, Hayes RL, Baglioni AJJ, Madden C (1998): Social skill as determinant of social networks and...
perceived social support in schizophrenia. Schizophr Res 29:275–286.


