Sensitivity to Intranasal Oxytocin in Adult Men with Early Parental Separation

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Background: Central oxytocin (OT) is critically involved in mediating social bonding and protecting against stress, depression, and anxiety. In animal models, early social experiences induce changes in central OT systems. In humans, early parental separation (EPS) increases the risk for emotional disorders in adulthood. We examined neuroendocrine responses to intranasal OT administration in men with EPS and healthy control subjects as an estimate of central OT sensitivity.

Methods: Salivary cortisol concentrations were measured in 9 healthy men with EPS and 10 control subjects before and after double-blind intranasal administration of placebo and OT (24 IU Syntocinon).

Results: Relative to placebo, intranasal OT resulted in attenuated cortisol decreases in EPS subjects compared with control subjects.

Conclusions: These preliminary results may suggest altered central sensitivity to the effects of OT after EPS. Future studies should replicate these results and scrutinize the role of OT in mediating risk versus resilience to psychopathology after early social adversity.

Key Words: Attachment, bonding, development, oxytocin, resilience, stress

A diverse childhood experiences, that is, early parental loss or separation, are major risk factors for the development of psychiatric disorders in adulthood, in particular, depression and anxiety disorders (Agid et al. 2000; Kendler et al. 1992). Positive social relations generally increase resilience against developing these disorders and promote health (House et al. 1988). Animal and human studies have provided evidence that the central oxytocin (OT) system is critically involved in mediating prosocial behavior, that is, social bonding, attachment, and trust (Insel and Young 2001; Kosfeld et al. 2005). Central OT furthermore exerts modulatory effects on neural circuits involved in the mediation of stress, depression, and anxiety and accordingly dampens neuroendocrine responses to stress (Engelmann et al. 2004; Legros 2001). The central OT system thus appears to play a key role in promoting resilience to the pathogenic effects of stress.

In animal models and clinical studies, early adversity is associated with increased physiologic stress responses, which are in turn related to behaviors or symptoms of depression and anxiety (Heim et al. 2004). Results from rodent studies suggest that early positive nurturing experiences as well as increased maternal care induce persistent changes in the central OT system (Francis et al. 2002). Alterations of the OT system as a consequence of early experience may contribute to individual vulnerability versus resilience to the pathologic effects of stress in humans. It is interesting that decreased urinary concentrations of OT have been measured in maltreated children (Fries et al. 2005). It is unclear to what extent peripheral measures may reflect central OT activity; however, it is also unclear whether the central OT system is altered in adults with early disruption of close social relationships.

Intranasal application is a suitable method to increase neuropeptide concentrations pharmacologically in the brain, as evidenced by cerebrospinal fluid studies (Born et al. 2002). Intranasal OT administration thus provides a useful approach to challenge central OT receptors. Accordingly, intranasal OT application results in neuroendocrine, neurofunctional, and behavioral responses in humans that are consistent with the functional role of OT (Heinrichs et al. 2003, 2004; Kirsch et al. 2005; Kosfeld et al. 2005). Because central OT dampens hypothalamic–pituitary–adrenal (HPA) axis activity, measures of peripheral cortisol concentrations before and after intranasal OT application relative to placebo may serve as a window into the brain’s OT sensitivity. We used this methodology to explore central OT changes in adult men with adverse childhood social experiences, that is, early parental separation (EPS).

Methods and Materials

Nineteen healthy young adult men aged 20 to 28 years, 9 with and 10 without EPS experience, were recruited from the student population of the University of Trier. Childhood adverse experiences were assessed using a standardized self-report questionnaire (Pennebaker and Susman 1988). To be assigned to the EPS group, subjects had to have experienced the divorce or permanent separation of their parents before age 13, and this must have resulted in prolonged separation from one parent. Although this form of EPS might appear a mild stressor relative to maltreatment or abuse, risk for adulthood depression is markedly increased after parental loss due to divorce or separation (Agid et al. 2000). Moreover, there is evidence for long-term neuroendocrine changes associated with EPS or high family conflict (Luecken and Lemery 2004; Meinlschmidt and Heim 2005). Control subjects could not have experienced any major childhood adversity, that is, abuse, molestation, neglect, loss, major accidents, or natural disasters. After complete description of the study, written informed consent was obtained. The study was approved by the Ethics Committee of the University of Trier. Only men were included to exclude gender differences and prevent adverse effects of OT in pregnant women.

All subjects underwent two testing sessions on 2 consecutive days. Each subject received intranasal placebo or OT (24 IU Syntocinon; Novartis; three puffs per nostril, each with four IU OT; Heinrichs et al. 2003, 2004; Kosfeld et al. 2005) in either session. The order of sessions was randomized and double-
Results

There was a significant difference in mean age between EPS and control subjects [25.2 (SD = 2.2) vs. 22.0 (SD = 2.3) years; \( t(17) = -3.16, p = .006 \)]. The mean age at the time of onset of EPS was 7.7 (SD = 4.4) years. Preapplication cortisol levels did not differ between groups or treatment conditions. There was a significant three-way interaction effect of the Group, Treatment, and Time factors \( F(4,68) = 5.62, p = .001 \), indicating differences in cortisol profiles over time in the OT versus placebo condition for EPS subjects compared with control subjects (Figure 1A). Regarding baseline-corrected indices of change after substance application, there was a significant two-way interaction effect of the Group and Treatment factors \( F(1,17) = 7.16, p = .016 \), indicating a difference in cortisol change between groups as a function of treatment type. Specifically, OT application relative to placebo resulted in marked declines of cortisol in control subjects but an attenuated decline in EPS subjects. Accordingly, placebo-corrected OT-induced change in cortisol concentrations was increased in EPS subjects but decreased in control subjects \( t = * t(17) = -2.68, p = .016 \; \text{Figure 1B} \). Because the groups differed significantly in mean age, we repeated all analyses including age as a covariate and results were confirmed [cortisol profiles: \( F(4,68) = 5.91, p < .001 \); baseline-corrected change index: \( F(1,16) = 5.224, p = .036 \); placebo-corrected OT-induced change index: \( F(1,16) = 5.244, p = .036 \)].

Discussion

We report preliminary results from a pilot study exploring central OT changes in adult men after socially disruptive experiences related to their parents’ relationship and parental availability during childhood. Because central OT dampens HPA axis activity, we combined intranasal OT application with serial measures of cortisol concentrations as an estimate of the brain’s sensitivity to OT. Compared to control subjects, men with EPS exhibited attenuated decreases in cortisol after OT application relative to placebo, potentially reflecting altered central sensitiv-
ity to the effects of OT after EPS. These results must be replicated in larger samples.

The precise mechanism of altered neuroendocrine responses to OT challenge after EPS cannot be determined from our study. Altered OT sensitivity as measured in this study likely involves changes at the OT receptor level, that is, altered receptor density, affinity, or function. Receptors involved in the anxiolytic and stress-protective effects of OT are localized in the paraventricular nucleus (PVN) of the hypothalamus, the central nucleus of the amygdala and the septum (Neumann 2002). In rodents, variations in maternal care modify OT receptor density in the central nucleus of the amygdala, the medial preoptic area, the PVN of the hypothalamus, and the bed nucleus of the stria terminalis (Francis et al. 2002).

Intranasal OT application reduces amygdala activation during fear-ful face processing in humans (Kirsch et al. 2005). Given that these brain regions are known to exert modulatory effects on HPA axis activation, it may be hypothesized that early social adversity in humans induces OT receptor changes in these regions, resulting in altered neuroendocrine responses to intranasal OT challenge. Alternative explanations for the observed effect may involve aberrant interactions between OT and other neurotransmitter systems that regulate the HPA axis or direct effects of OT on pituitary corticotrophic cells. Future studies should employ functional imaging in combination with intranasal OT challenge as well as radioligand OT receptor neuroimaging to further scrutinize central OT changes after early social adversity. Further corroboration for altered central OT sensitivity may be obtained by measuring behavioral changes, that is, mood state, anxiety, and social cognition after OT challenge.

Differences between study groups other than EPS may have contributed to the effects, which should be addressed in future studies.

In conclusion, altered central OT sensitivity might interfere with protection against stress, promotion of health, and social adaptation, thereby contributing to individual vulnerability to psychiatric disorders after early social adversity. If replicated, these results may support the development of novel therapeutics targeting the central OT system to prevent pathologic effects of early loss and promote resilience against stress. Investigating protective neurobiological systems involved in resilience against psychiatric disorders is a critical next step in psychiatric research (Charney 2004). We hope that our findings might serve as an impetus for future research on protective neuropeptide systems in clinical samples.

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