Preventing PTSD with oxytoxin
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Promoting resilience after trauma: clinical stimulation of the oxytocin system

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Traumatic experiences that threaten a person’s life or physical integrity and evoke a response of fear, helplessness, or horror, are a common phenomenon. In the Netherlands, approximately 80% of people experience a potentially traumatic event at least once during their lifetime. Of these, approximately 10% develop psychological symptoms that meet the criteria for posttraumatic stress disorder (PTSD) (de Vries and Olff, 2009). PTSD is characterized by symptoms of re-experiencing the traumatic event, avoiding reminders of the event, hyperarousal, and emotional deficits such as emotional numbing (American Psychiatric Association, 2000). Present evidence-based early interventions for PTSD treat this condition after symptoms have developed (Veterans Health Administration-Department of Defense, 2010). A practice that would apply therapeutic intervention at an earlier stage in order to prevent the onset or the aggravation of PTSD symptoms would be greatly desirable. At the present time some early interventions appear to be effective (e.g. Zohar et al., 2011). However, these have not been tested sufficiently to meet evidence-based criteria.

The ability to distinguish resilient from vulnerable trauma-exposed individuals may be important for the development of novel interventions to prevent PTSD. Modifiable risk factors may be identified and targeted for early interventions. Among the strongest and most consistently found predictors of PTSD is a lack of perceived social support posttrauma. In addition, inadequately regulated stress and fear responses seem to underlie the development of PTSD. These risk factors for PTSD may be suitable targets for early interventions.

Oxytocin (OT) is a mammalian neuropeptide that supports social bonds and affiliation and that regulates stress and fear responses. In this chapter, we will discuss evidence that stimulation of the OT system is a promising clinical approach to promote resilience posttrauma, by regulating stress and fear responses and improving feelings of social support.
PROCESSES INVOLVED IN THE DEVELOPMENT OF PTSD: SOCIAL SUPPORT AND STRESS AND FEAR RESPONSES

Social support and the development of PTSD

Studies have established that a subjective lack of social support following trauma is a strong predictor of the development of PTSD. A lack of social support can either result from the presence of negative social interactions or the absence of positive social reactions. Both have been found to be associated with increased risk for the development of PTSD (Robinaugh et al., 2011). In addition, findings suggest that childhood trauma and its associated insecure attachment are related to increased risk for PTSD and the ability to benefit from social bonds (Charuvastra and Cloitre, 2008). Increasing social support at an early phase following trauma may change an adverse course into a more resilient trajectory (Olff, 2012).

Stress and fear responses and the development of PTSD

Since Walter Cannon’s fight-flight formulation, a century of research on stress and fear has established that psychological stress results in the activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. The activity levels of these systems usually restore to baseline levels after the stressor has disappeared. However, functioning of these systems may be dysregulated during and after traumatic experiences, as demonstrated in the extensive literature since the establishment of the PTSD diagnosis in 1980 (Pole et al., 2009; van Zuiden et al., 2013).

Prospective studies have assessed sympathetic, parasympathetic, and HPA axis changes at an early phase after trauma and the subsequent development of PTSD symptoms. These studies showed that high heart rate (e.g. Coronas et al., 2011), lower heart rate variability (e.g. Shaikh al arab et al., 2012), and low cortisol levels (for review see van Zuiden et al., 2013) were predictive of the development of PTSD in adults, although these findings have not been consistent.

Studies have also considered pretrauma vulnerability factors that are associated with the development of PTSD. Pre-existing high startle responses to threat (e.g. Pole et al., 2009) predicted PTSD symptoms following a traumatic experience. In addition, pretrauma measures of HPA axis functioning and amygdala reactivity have been associated with increased PTSD risk post-deployment in military personnel (for review see van Zuiden et al., 2013). Thus, studies of stress and fear mechanisms involved in PTSD development have shown alterations...
in these systems in vulnerable individuals exposed to trauma. These alterations may represent insufficient stress and fear regulation in the face of a traumatic experience. Resilience to PTSD could be promoted by improving adaptive regulation of stress and fear responses during the early phase following exposure to trauma.

**LINKS BETWEEN SOCIAL SUPPORT, STRESS, AND FEAR RESPONSES**

Presence or absence of social support modulates stress and fear in a number of studies. The presence of a familiar supportive person attenuated heart rate responses while experiencing a psychosocial stressor (i.e. a public speech task) compared to the presence of a stranger or no one present (e.g. Lepore et al., 1993). Men who perceived instrumental and emotional support from their partners, showed diminished cortisol responses to a psychosocial stressor compared to controls who did not receive support (Kirschbaum et al., 1995). In women with metastatic breast cancer, those with a greater perceived quality of social support had lower diurnal salivary cortisol levels (Turner-Cobb et al., 2000). Consistent with these findings, a neuroimaging study demonstrated that handholding diminished brain activity in areas related to threat processing (Coan et al., 2006). The magnitude of this decrease depended on the quality of the relationship with the handholder.

Early social experience may alter fear and stress responses later in life. Human studies for example showed that adverse social interactions during development, such as maltreatment and interpersonal adversity, were associated with adult altered cortisol and heart rate responses to stressors (Lovallo et al., 2012).

**STIMULATING THE OXYTOCIN SYSTEM TO PREVENT PTSD**

The neuropeptide OT is widely distributed in the brain (Gautvik et al., 1996). As a hormone endogenous OT is released into the bloodstream where it acts as a smooth muscle contractor involved in e.g. childbirth and lactation. The past few decades have seen a burgeoning of research on the role of OT in social behavior. In pioneering studies in the monogamous prairie vole, OT facilitated pair-bonding and partner preference (Carter et al., 1992). In human studies OT is involved in mother-infant bonding (Galbally et al., 2011) and others forms of parental behavior (Feldman et al., 2011). OT is released during safe social contact, such as vocal socialization of a mother to her child (Seltzer et al., 2010), and massage (e.g. Rapaport et al., 2012).
In studies of the novel application of intranasal OT, results showed that OT facilitates trust and prosocial behavior (for a review see van IJzendoorn and Bakermans-Kranenburg, 2012). By attenuating HPA axis (Altemus et al., 1995) and sympathetic activity (Light et al., 2005) OT demonstrated a significant role in modulating physiological stress. Findings showed that in humans intranasal OT decreased HPA axis responsivity (Markus Heinrichs et al., 2003) and increased parasympathetic responsivity (Norman et al., 2011). Intranasal OT also dampened amygdala activity (e.g. Domes et al., 2007) and enhanced functional connectivity between the amygdala and the prefrontal cortex (C. S. Sripada et al., 2012) thereby indicating that intranasal OT may increase fear regulation.

Due to the observed effects of OT on social behavior and on stress and fear responses, OT activity appears to serve important neurobiological underpinnings of the effects of social support on the reactivity of stress and fear (Uvnas-Moberg, 1998). Based on these well-documented findings, we propose that the stimulation of OT will have a preventive role in the development of PTSD (Figure 2.1).

The effectiveness of intranasal OT in preventing PTSD is being studied in an ongoing randomized controlled trial (RCT) in our center in Amsterdam. Two studies have examined the acute effects of intranasal OT in patients who already have developed PTSD. Pitman and colleagues (1993) reported on the effects of intranasal OT on sympathetic reactivity in PTSD patients. In this study, intranasal OT, arginine vasopressin (a neuropeptide very similar to OT in structure), or placebo were administered to veterans with and without PTSD. Results showed that sympathetic reactivity to personal combat imagery was lower in both groups after OT administration compared to intranasal placebo or arginine vasopressin (Pitman et al., 1993). The second study was a pilot report on a single administration of OT administrated to patients with PTSD. Eighteen patients with PTSD were treated with both intranasal OT and placebo in a within-subject design. Fifty minutes after the administration of OT, findings showed lowered anxiety, tension, restlessness, and irritability, as well as improved mood and the desire for social interaction. These were associated with a small reduction of acute PTSD symptoms compared to intranasal placebo (Yatzkar and Klein, 2009). Comparable findings were obtained in a rodent study. Central OT administration immediately or seven days after a severe stressor was associated with reduced PTSD-like behavior in rats one week after administration in comparison to the control condition (Cohen et al., 2010). Interestingly, central OT administration in mice prior to fear conditioning subsequently facilitated fear extinction (Toth et al., 2012). These findings support the development of OT stimulation treatments for the prevention of PTSD.
Figure 2.1

Schematic overview of the hypothesized effects of oxytocin stimulation on the prevention of PTSD.

This figure shows how stimulation of the OT system following trauma targets risk factors associated with PTSD, i.e. inadequate regulation of stress and fear responses and lack of perceived social support. There are two ways to stimulate the OT system: intranasal OT administration and the provision of safe social contact (social support intervention). Both methods of stimulating OT should affect endogenous OT activity, which are predicted to result in the regulation of stress and fear responses. Improved regulation of stress and fear are expected to turn an adverse course into a more resilient recovery, which may result in preventing the development of PTSD.
OXYTOCIN STIMULATION TREATMENT APPROACHES

Intranasal oxytocin treatment

There is good evidence that intranasal OT administration stimulates the endogenous OT system. Administration of intranasal OT results in increased peripheral OT levels that last for a considerable length of time (at least for seven hours), an effect attributed to a feed-forward cascade that increases endogenous OT release following intranasal OT administration (van IJzendoorn et al., 2012).

There are no established guidelines yet on the dose and duration of intranasal OT application for optimal effects. The doses most commonly used in clinical OT studies are 24 and 40 International Units (IU). However, little is known about the differential effects of these doses (MacDonald et al., 2011). The longest reported time period of continued use of intranasal OT in an RCT was 13 weeks in patients with chronic constipation, in whom it was hypothesized that OT’s smooth muscle contracting properties would decrease abdominal symptoms (Ohlsson et al., 2005). In a report on the effects of intranasal OT on sexual functioning OT was administered for several months and continued stable benefits without discernable adverse effects were reported (Macdonald & Feifel, 2012). A review showed that short-term use (up to three weeks) of daily or twice-daily intranasal OT up to 40 IU produced minimal side-effects, both in healthy individuals and psychiatric patients. In addition, groups receiving OT or placebo did not differ in number and severity of side-effects (MacDonald et al., 2011).

Increasing social support

Novel interventions aimed at increasing social support are currently being tested for their effectiveness in preventing PTSD. For example, Psychological First Aid (PFA) was created as an evidence-informed early intervention in the acute aftermath of disasters. PFA provides a guideline for professionals or volunteers who face exposed individuals after a traumatic event and who want to offer both psychological and material support. Based on the observation that a perceived lack of social support is a strong predictor of PTSD, providing acute social support and connecting individuals with their loved ones is an important part of this (National Child Traumatic Stress Network, 2005). However, no studies on the effectiveness of PFA in preventing PTSD have appeared in the literature.

We propose that the aim of a preventative social support intervention should be twofold: to provide acute safe social contact and to promote the use of the available social support from one’s own environment. The provision of safe social contact by the professional provides a
general non-threatening social environment, creates social support, and increases endogenous OT activity, as supported by studies on safe social context and increased peripheral OT levels. Furthermore, creating awareness of specific personal needs with regard to social support as well as exploring means for meeting those needs may result in new resilient coping skills. These may lead to more effective supportive social contexts and to the building of more stable positive social supports. Significant others of those individuals exposed to trauma may be part of an intervention. In such a dyadic social support intervention, the aim should be to strengthen already existing supportive behaviors and to explore ways of meeting common supportive needs. One limitation of social support stimulating interventions is that they may only apply to those who have an available social network. However, in trauma-exposed individuals who experience a lack of support but do not have supportive ties, the therapist may explore other avenues of support, including victim self-help groups, internet connections, or the company of pets. The latter have shown beneficial effects induced by OT activity (Beetz et al., 2012).

A social support intervention should ideally consist of two or three sessions and should be easy to administer. This will allow different professionals working in mental health care settings to follow a simple protocol in providing the intervention.

Finally, a combination of the two methods to stimulate OT activity may also be used. In order to enhance receptiveness to a psychological intervention, intranasal OT could be administered prior to a session (Olff et al., 2010). Pre-session OT may result in increased OT release due to a positive feedback mechanism (van IJzendoorn et al., 2012), increased readiness to engage socially, and promote a trustful relationship with the therapist, which may make the intervention more effective.

METHODOLOGICAL CONSIDERATIONS IN OXYTOCIN STIMULATION APPROACHES

Target populations

In order to effectively prevent the development of PTSD, the intervention should be aimed at recently traumatized individuals. It should be noted that various traumas do not come to the immediate attention of health care professionals and not all trauma-exposed individuals will be readily identified for early interventions. Survivors of traffic accident requiring medical attention and individuals at high risk for exposure to trauma (i.e. military personnel, police, etc.) have most often been treated in early intervention studies. Survivors of disasters are also relatively easy to identify for early intervention.
Early interventions require clear selection procedures. Since the majority of individuals exposed to trauma will actually not develop PTSD, only those with increased risk for PTSD should receive the intervention. The identification and selection of individuals at increased risk for PTSD should be based on established information on vulnerability and resilience factors. At this stage, known biological risk factors cannot be used in the identification of individuals at risk, since optimal cutoffs and the timing of assessments have not been reliably and validly established. In addition, these measures are not easy to obtain. An alternative is the use of validated surveys to distinguish high-risk from low-risk trauma-exposed individuals that assess self-reported risk factors at pretrauma, peritrauma and posttrauma stages. One drawback is that questionnaires may be influenced by purposeful or unintentional distortion in comparison to biological measures. An optimal future approach may combine both biological and psychological measures in risk assessments.

With regard to intranasal OT, contraindications should be considered prior to treatment. Pregnant or breast-feeding individuals exposed to trauma cannot receive intranasal OT, since OT may cause uterine contractions and breast milk secretion (MacDonald et al., 2011).

**Timing**

An optimal time for the prevention of PTSD stipulates that intervention occur within the first 6 hours posttrauma, the so-called ‘golden hours’. These 6 hours are important in the consolidation of traumatic memory (Zohar et al., 2009). The same research group investigated effects of central OT administration either 1 hour or 1 week after severe stress exposure in rats. At both time points OT reduced PTSD-like behavior in comparison to control vehicle-treated animals (Cohen et al., 2010). This finding implies that OT stimulating interventions may still be effective in reducing PTSD-like behavior after the golden hours have passed, thereby providing broader opportunities to treat trauma-exposed individuals.

So far we have discussed preventive interventions to be administered posttrauma. In theory, preventative measures could also be applied pretrauma to populations at high risk of exposure to trauma, such as military personnel or police employees. In these populations OT would have to be administered frequently for a prolonged period of time, since the time of trauma exposure is often unexpected. However, health effects of prolonged OT administration would have to be thoroughly investigated beforehand.
Context and individual factors

Important considerations when implementing intranasal OT in a clinical application are the effects OT administration has on contextual and interindividual factors (J. A. Bartz et al., 2011). Clinical studies using intranasal OT and/or social support should evaluate the influence of these factors in their subgroups before any of these interventions can become general practice. Effects of OT reveal a variety of sex differences. For example, neuroimaging studies show that OT administration in females increased amygdala activation to emotional faces (Domes et al., 2010). By contrast, men show decreased amygdala activation after intranasal OT (Domes et al., 2007). In addition, salivary alpha-amylase levels (a measure of sympathetic activity) decreased in women during couple conflict conditions after OT administration, whereas alpha-amylase levels increased in men (Ditzen et al., 2012). It is possible that similar sexually dimorphic effects may be observed in the effects of a social support intervention.

Other interindividual factors complicate the effects of OT further. De Dreu and colleagues (Dreu et al., 2010) observed that, following intranasal OT, participants donated more money only to their in-group members. By contrast, out-group members received less money (De Dreu et al., 2010). Several studies showed that OT’s prosocial effects acted mainly through in-group (van IJzendoorn and Bakermans-Kranenburg, 2012). These findings may have implications for the application of intranasal administration of OT to trauma-exposed individuals in relation to their personal in-group and out-group perceptions.

Consideration should also be given to the influence of attachment on the effectiveness of interventions that stimulate OT. In a study on perceptions of maternal closeness, the authors observed that less anxiously attached individuals remembered their mothers as more caring after OT administration, whereas those who were more anxiously attached, remembered their mother as less caring after intranasal OT (J A Bartz et al., 2010). In other studies, intranasal OT was effective for those individuals who could gain with regard to social functioning. Intranasal OT improved empathetic accuracy only in individuals with poorer social-cognitive performance in comparison to those with better social-cognitive performance (Jennifer A Bartz et al., 2010). Intranasal OT attenuated cortisol levels only in those with low emotion regulation abilities, but not in individuals with high emotion regulation abilities (Quirin et al., 2011).

It has been proposed that OT increases the salience of social cues. Salience depends on interpersonal and contextual factors (J. A. Bartz et al., 2011). This may explain the selective effects of intranasal OT administration. Therefore, when studying the effects of OT stimulating interventions posttrauma, individual characteristics and social perceptions of trauma-exposed individuals should be assessed, in order to identify those factors that account for the intervention’s effectiveness.
CONCLUSIONS

The development of PTSD is associated with a lack of perceived social support and with inadequate regulation of stress and fear responses. The current review shows that these risk factors may be modifiable and that they may be suitable targets for early intervention to prevent the development of PTSD in individuals exposed to trauma. Interestingly, social behavior and the functioning of HPA axis, sympathetic, parasympathetic, and cortico-limbic fear mechanisms are closely interconnected and are all influenced by OT. OT can be administered intranasally and is safe to use. In addition, OT release may be stimulated endogenously by the provision of safe social contact, such as therapeutic social support settings. A promising area of research is the effectiveness of OT stimulating interventions, applied in the aftermath of a traumatic event prior to the development of the full-blown constellation of PTSD symptoms. In this context, attention needs to be paid to contextual and interindividual influences on the effects of OT. The timing of the intervention and dose of OT stimulation should be assessed to establish maximal efficacy. In conclusion, we propose that OT stimulating interventions administered early after trauma are a promising treatment approach and are easily applied in order to restore an adaptive resilient response in individuals with PTSD.