Preventing PTSD with oxytoxin
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1 General Introduction
Exposure to psychological trauma is a common phenomenon. It can happen to anyone, as approximately 70% of the worldwide general population experiences at least one traumatic event during their lifetime (Benjet et al., 2015). In the latest Diagnostic and Statistical Manual of Mental Disorders (DSM-5) a traumatic event is defined as direct or indirect exposure to actual or threatened death, serious injury or sexual violence (American Psychiatric Association, 2013). Examples of traumatic events are motor vehicle accidents, physical or sexual assault, combat exposure, and natural disasters. A trauma-exposed individual may initially experience distress, such as feeling fearful when thinking of the event, or difficulties concentrating and sleeping. These initial reactions are considered to reflect normal, adaptive responses to trauma. In the majority of trauma-exposed individuals, these acute posttraumatic reactions naturally subside over the course of a few weeks, and do not result in long-term dysfunction.

However, approximately ten percent of trauma-exposed individuals develops posttraumatic stress disorder (PTSD) (de Vries and Olff, 2009; Kessler et al., 2012). The hallmark symptom of PTSD constitutes intrusive re-experiencing of the traumatic event (e.g. nightmares, flashbacks, intrusive memories of the trauma). Besides re-experiencing, PTSD patients avoid trauma-related stimuli, and exhibit persistent negative alterations in mood and cognition, as well as in arousal and reactivity associated with the traumatic event (American Psychiatric Association, 2013). If PTSD symptoms are present for least one month, and result in functional impairment in social, occupational or other important domains, a formal PTSD diagnosis can be made. Once PTSD has developed, without adequate and timely treatment there is an increased risk of a chronic course (Bryant et al., 2015). PTSD is not only a burden for the affected individual and his/her immediate surroundings, but may also be considered a public health issue (Magruder et al., 2016). PTSD is associated with the highest health care costs compared to other anxiety disorders (Marciniak et al., 2005), which even further increase in case of comorbid major depression disorder or substance use disorder, which are both highly prevalent in PTSD patients (Kessler et al., 2012; Marciniak et al., 2005; McCauley et al., 2012). PTSD is also associated with somatic morbidity (Koenen et al., 2016) and increased health care utilization (Calhoun et al., 2002; Richardson et al., 2006).
Evidence-based treatments for PTSD include trauma-focused psychotherapy (e.g. cognitive behavior therapy (CBT), eye movement desensitization reprocessing (EMDR)) and treatment with selective serotonin reuptake inhibitors (SSRIs) (Forbes et al., 2010). However, in a study in the general population, almost 93% of PTSD patients did not seek treatment within the first year of symptoms (Wang et al., 2005). Furthermore, these therapies are not sufficiently effective in about one-third of patients (Bradley et al., 2005; Pull and Pull, 2014). Therefore, substantial effort should be made to minimize the individual and societal burden associated with PTSD (Olff et al., 2015a).

Secondary prevention of PTSD is a promising approach to reduce the burden associated with PTSD, as effective prevention results in fewer trauma-exposed individuals developing (chronic) PTSD. As trauma exposure constitutes an identifiable event of potential PTSD onset, the first hours to weeks posttrauma serve as a suitable time-period for the provision of early preventive interventions for PTSD, aimed to reduce subsequent PTSD symptom development. Previously, administration of benzodiazepines (Gelpin et al., 1996; Mellman et al., 2002), SSRIs (Galatzer-Levy et al., 2013) and the beta-adrenergic receptor blocking agent propranolol (Hoge et al., 2012; Stein et al., 2007) early posttrauma did not reduce subsequent PTSD symptom development in recently trauma-exposed individuals. Similarly, psychological debriefing within the first weeks posttrauma was ineffective in preventing subsequent PTSD; there are even indications that debriefing increased PTSD symptoms in some individuals (Rose et al., 2002; Sijbrandij et al., 2006). Current early interventions that hold significant promise for effective PTSD prevention (i.e. hydrocortisone administration (Delahanty et al., 2013; Zohar et al., 2011) prolonged exposure therapy (Rothbaum et al., 2012) and brief CBT (Roberts et al., 2009), are not yet at the stage of widespread implementation, as clinical evidence supporting their efficacy is still sparse (Sijbrandij et al., 2015). Therefore, it remains highly relevant to further study novel preventive interventions for PTSD.

One potential strategy for novel preventive interventions for PTSD is to pharmacologically target neurobiological and socio-emotional risk factors for PTSD early posttrauma that are likely to be etiologically involved in PTSD development. In recent years, it was observed that autonomic and glucocorticoid reactivity to stress, assessed prior to or early posttrauma, predicted PTSD symptom development (Coronas et al., 2011; Pole et al., 2009; van Zuiden et al., 2013). Also, pre- and early posttrauma hyperreactivity of the amygdala – a brain region with a pivotal role in detection, expression, regulation and learning of fear – was found to predict subsequent PTSD symptoms (Admon et al., 2009; McLaughlin et al., 2014). Furthermore, low perceived social support early posttrauma has been associated with increased PTSD risk (Brewin et al., 2000). Intranasal administration of the neuropeptide oxytocin (see box 1.1 for additional background information) is a promising pharmacological agent for PTSD prevention (Olff, 2012). Accumulating evidence from studies in animals and in human populations
with and without psychiatric disorders shows that oxytocin administration may modulate autonomic stress reactivity (Kubzansky et al., 2012), attenuate anxiety and amygdala reactivity (Kirsch et al., 2005a; S B Koch et al., 2016), as well as beneficially impact socio-emotional processes and pro-social behavior (Preckel et al., 2014; van IJzendoorn and Bakermans-Kranenburg, 2012. Given these beneficial effects of oxytocin administration on factors associated with increased PTSD risk, it was hypothesized that administration of intranasal oxytocin early posttrauma may prevent subsequent PTSD symptom development (Olff, 2012).

**BOX 1.1 – OXYTOCIN**

Oxytocin is a mammalian neuropeptide and is synthesized in the periventricular and supraoptic nuclei of the hypothalamus. It is released into the circulation from the posterior pituitary. Neuronal projections from the hypothalamus send oxytocin to other brain regions. In humans, brain regions that express the oxytocin receptor – and thereby are likely affected by oxytocin – include the central and basolateral amygdala, brainstem, olfactory nucleus, and anterior cingulate cortex (Boccia et al., 2013). In rest, peripheral oxytocin levels are comparable between men and women (de Jong et al., 2015; Feldman et al., 2010; Graugaard-Jensen et al., 2014).

Oxytocin is physiologically involved in parturition and lactation by acting as a smooth muscle contractile on the uterus and lactation glands. In the nineties, pioneering work in prairie voles – socially monogamous rodents that are similar to humans in their tendency and ability to form strong social pair bonds – demonstrated that oxytocin is a crucial neurobiological mediator of social pair bond formation and maternal behavior. Subsequently, studies in humans demonstrated oxytocin’s involvement in trust, attachment, empathy, paternal behavior and romantic relationships (Feldman, 2012). As a result, popular media – and also scientists (Carter, 1998; Neumann, 2007; Olff et al., 2015b) – often reference to oxytocin as the ‘cuddle’, ‘love’, or ‘miracle’ hormone. As oxytocin also appeared to have anti-stress (Cardoso et al., 2014; Markus Heinrichs et al., 2003) and anxiolytic properties (Huber et al., 2005; Kirsch et al., 2005a; Knobloch et al., 2012; Viviani et al., 2011) – and most psychiatric disorders are associated with both social dysfunction and aberrant stress reactivity – the attention of researchers within psychiatry was definitely drawn. A novel research field grew investigating potential clinical applications of intranasal oxytocin administration in psychiatric populations. This has not only yielded a large body of studies on intranasal oxytocin effects on a wide variety of socio-emotional and neurobiological outcome measures, but has also resulted in more critical, nuanced views of the clinical potential of intranasal oxytocin administration (Carson et al., 2016; Leng and Ludwig, 2016), compared to the early overly positive views – or hopes – regarding the effects of intranasal oxytocin administration for clinical purposes.
GENERAL AIMS AND OUTLINE

The overall aim of the current PhD-thesis was to investigate the potential of intranasal oxytocin administration as early preventive intervention for PTSD, by assessing the effects of intranasal oxytocin early after trauma on functioning of the fear neurocircuitry and on PTSD symptom development in recently trauma-exposed individuals. To this end, we performed a functional magnetic resonance imaging (fMRI) study to assess the acute effects of a single administration of oxytocin on the functional fear neurocircuitry – consisting of the amygdala and (pre)frontal brain regions associated with fear extinction and emotion regulation – in recently trauma-exposed emergency department patients. In addition, we performed a randomized controlled trial to assess the efficacy of repeated intranasal oxytocin administration early after trauma for preventing the development of PTSD symptom. Furthermore, we investigated neurobiological correlates of PTSD and acute PTSD symptoms.

Part I - Background
In chapter 2 we further introduce PTSD vulnerability factors and oxytocin administration effects, and expand on the rationale of using oxytocin administration for PTSD prevention. Importantly, in recent years it became increasingly apparent that effects of intranasal oxytocin cannot be generalized to all individuals and contexts. In chapter 3 we aimed to review and describe findings showing that effects of intranasal oxytocin are moderated by context and interindividual differences, which constitutes important evidence for the hypotheses of our clinical study. We discuss whether context and interindividual dependent effects of oxytocin administration may be related to the effects of oxytocin on salience processing, i.e. the processing of contextual cues that normally attract attention.

Part II – Functional neuroimaging studies
In recently trauma-exposed emergency department patients we performed an fMRI study in which we aimed to investigate the effects of a single intranasal oxytocin administration on fear neurocircuitry, including amygdala reactivity and amygdala functional connectivity. Chapter 4 describes the experiment in which we assessed the effects of oxytocin administration on amygdala reactivity to emotional faces. Chapter 5 describes a second functional neuroimaging paradigm, in which we investigated whether oxytocin administration affected amygdala resting-state functional connectivity with brain regions associated with emotion regulation and salience processing in response to trauma script-driven imagery.
Part III – Randomized controlled clinical trial
We performed a randomized double-blind placebo-controlled clinical trial in recently trauma-exposed emergency department patients. We aimed to investigate the effects of repeated intranasal oxytocin administration on the development of PTSD symptoms up to 6 months posttrauma. Chapter 6 outlines the protocol of this study and in chapter 7 the results are presented.

Part IV – Neurobiological correlates of PTSD and acute PTSD symptoms
To better target novel preventive interventions for PTSD, knowledge on neurobiological correlates of (vulnerability for) PTSD is crucial. Chapter 8 describes a diffusion tensor imaging study in which we aimed to assess whether acute PTSD symptom severity was associated with white matter integrity of white matter tracts previously associated with PTSD vulnerability. Furthermore, in chapter 9 we investigated whether basal salivary oxytocin levels differed between police officers with and without PTSD.

Finally, chapter 10 provides a summary of the chapters in this thesis, as well as an integrated discussion of our findings.