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Review article

Meta-analytic review of the effects of a single dose of intranasal oxytocin on threat processing in humans

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ABSTRACT

Background: Heightened threat sensitivity is a transdiagnostic feature in several psychiatric disorders. The neuropeptide oxytocin has been shown to reduce fear related behaviours and facilitated fear extinction in animals. These findings have led to increasing interest to explore the effects of intranasal oxytocin on threat processing in humans.

Methods: The review included 26 studies (N = 1173), nine of which included clinical populations (N = 234). The clinical groups included were people with borderline personality disorder (BPD), anorexia nervosa, bulimia nervosa, depression, anxiety, and alcohol dependence disorder. We examined the effects of a single dose of intranasal oxytocin on startle response, attentional responses, and behavioural responses to threat.

Results: A single dose of intranasal oxytocin significantly increased the physiological startle response to threat in healthy people with a small effect size. However, oxytocin did not have significant effects on attentional bias towards social or disorder-specific threat, fixation towards threatening stimuli among healthy or clinical populations, or on threat related behavioural approach or avoidance responses.

Limitations: No studies investigated the effects of oxytocin on the startle response to threat among clinical populations. Additionally, only one of the reviewed studies had sufficient power to detect at least a moderate effect of oxytocin according to our criterion.

Discussion: The synthesis of literature suggest that oxytocin may influence the salience of threatening stimuli among healthy individuals, increasing the startle response to threat. It would be of interest to investigate the effects of oxytocin on the startle response to threat among clinical populations.

1. Introduction

Threat processing is vital for the survival of an organism or species (Öhman, 2005, 2007). Potential threats are rapidly recognised and activate a number of subcortical structures including the amygdala and the hypothalamic-pituitary-adrenal (HPA) axis, which initiate protective fear responses (Öhman, 2005). Physiological responses, such as increased skin conductance, behavioural approach and avoidance responses, such as fight or flight responses, and attentional responses, such as active attending to the source of fear also occur (Misslin, 2003). However, hypersensitivity of this system and maladaptive fear learning can have negative consequences (Ozawa and Johansen, 2014). Such maladaptive processes are believed to contribute to the development and maintenance of number of psychiatric disorders, such as eating disorders (ED), anxiety disorders, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) (Britton et al., 2011; Ozawa and Johansen, 2014; Strober et al., 2007).

Behavioural studies have demonstrated that people with PTSD, OCD, and ED show anomalies in physiological responses to threat. For example, there is an exaggerated physiological startle response to anticipation and viewing of disorder-specific, potentially threatening stimuli, such as images of trauma, contamination, or food (Altman et al., 2013; Mauler et al., 2006; Pitman et al., 2012; Simon et al., 2013). Additionally, a number of reviews have reported atypical attentional bias towards disorder specific stimuli (Bar-Haim et al., 2007; Brooks et al., 2011; Cisler and Koster, 2010). Furthermore, disorder specific stimuli have been found to elicit negative facial expressions and subjective feelings of fear and disgust (Broderick et al., 2013; Soussignan

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et al., 2011; Uher et al., 2004). Taken together these findings suggest that treatments targeting this hypersensitivity and maladaptive fear learning may be of benefit in these disorders.

The neuropeptide, oxytocin, has been found to play an important regulatory role in human and animal studies (Neumann and Slattery, 2016; Onaka et al., 2012; Zheng et al., 2010). Animal studies have demonstrated that oxytocin plays an important role in lowering the physiological stress and anxiety response by activating a negative feedback loop (Onaka et al., 2012; Zheng et al., 2010). Elevated oxytocin secretion from the paraventricular nucleus of the hypothalamus following a stressful event is believed to lead to increased availability of gamma-aminobutyric acid (GABA), which in turn is believed to inhibit the HPA axis and amygdala activation (Onaka et al., 2012; Zheng et al., 2010). Indeed, a recent study found that marmoset monkeys treated with an oxytocin receptor antagonist had elevated glucocorticoid levels in response to the stressor and showed a greater tendency to engage in maladaptive fear-related behaviour such as isolation (Cavanaugh et al., 2016). These findings have sparked increasing interest in exploring the role of oxytocin in threat processing, particularly in fear responses and extinction learning.

Preclinical studies have demonstrated that exogenous intravenous and intranasal oxytocin can influence fear related responses in rodents and monkeys respectively, reducing hiding behaviour during an open field test and attentional bias towards threatening facial expressions (Parr et al., 2013; Rotzinger et al., 2010). Additionally, a recent systematic review explored the role of the oxytocin system in fear extinction in rodents (Neumann and Slattery, 2016). The findings revealed that oxytocin reduced fear related behaviours and facilitated fear extinction in rodents, particularly when the exogenous oxytocin or oxytocin agonists were administered to the infralimbic cortex (Neumann and Slattery, 2016). The infralimbic cortex has inhibitory projections to a number of subcortical regions in the rodent brain including the amygdala and activation of this region has been documented to be associated with fear extinction in rodents and humans (Quirk and Beer, 2006). These findings suggest that oxytocin may reduce fear and facilitate extinction possibly by reducing stress and anxiety around the source of potential threat. Thus, these findings have led to increasing interest to investigate the role oxytocin plays in threat processing and fear extinction in humans as well as its therapeutic potential in disorders characterised by elevated threat sensitivity and resistance to natural extinction.

A few studies have begun to explore the effects of intranasal oxytocin on threat processing and the physiological stress and anxiety response in humans. For example a recent meta-analysis found that a single dose of intranasal oxytocin lowered cortisol in clinical populations characterised by dysregulation of the HPA axis, but did not significantly influence the cortisol response to stressful stimuli in healthy individuals (Cardoso et al., 2014). Since many psychiatric disorders, including ED, PTSD, and anxiety disorders, are characterised by dysregulation of the HPA axis (Connan et al., 2007; Ehlert et al., 2001; Lo Sauro et al., 2008), there has been increasing interest in further exploration of the potential anti-stress and anxiolytic effects of intranasal oxytocin. To our knowledge, no systematic reviews have thus far investigated the effects of single dose of intranasal oxytocin on different aspects of threat processing in healthy and clinical populations more broadly.

The aim of the current systematic review and meta-analyses was to build on previous literature and synthesise studies examining the effects of a single dose of intranasal oxytocin on threat processing among in humans. The objective was to investigate the effects of oxytocin on the physiological startle response, behavioural approach and avoidance responses, and attentional responses, including attentional bias and fixation, towards generally threatening stimuli as well as towards disorder related threatening stimuli among clinical populations. Based on findings outlined above, we hypothesised that a single dose of intranasal oxytocin would reduce these anomalous threat responses in clinical populations characterised by elevated threat sensitivity.

2. Methodology

2.1. Literature search

In accordance with the PRISMA guidelines (Moher et al., 2009), electronic databases, including OVID (PsycINFO, PsycARTICLES, Medline, ARGIS), Web of Knowledge core collection, and Pubmed, were searched April 2017. The search terms included *oxytocin AND (threat OR fear OR anxiety OR avoidance OR attention OR bias OR startle OR approach OR fixation OR gaze)*. Furthermore, bibliographies of included studies were inspected to look for further studies not yielded by the initial search.

2.2. Inclusion criteria

In order to be included in the systematic reviews and meta-analyses studies were required to meet the following inclusion criteria: 1) investigate physiological response, behavioural approach and avoidance response, attention, or fixation towards threatening or feared stimuli; 2) investigate the effects of a single dose of intranasal oxytocin on these measures; 3) compare the effects of intranasal oxytocin against intranasal placebo; 4) include healthy adult participants and/or adult clinical populations; 5) random allocation of participants to receive intranasal oxytocin or placebo in studies using between subjects design; 6) randomisation of treatment order in studies using within subjects design; 7) be published in English in a peer reviewed journal. In order to reduce heterogeneity, long trials in which participants received more than one dose of oxytocin or in which effects of oxytocin were investigated the following day or later were not included.

2.3. Study selection

The search flow diagram is presented in Fig. 1. The literature search and initial screening based on title and abstract was conducted by the first author. The full text articles identified in the initial search and screening were examined for eligibility by two authors in conjunction (J.L. and K.W.N.). Studies were then included in the systematic review and meta-analyses if both authors agreed they met the inclusion criteria. If there was any uncertainty regarding eligibility of a paper it was referred to the rest of team for further discussion.

2.4. Data collection and synthesis

We conducted three separate meta-analyses investigating the effects of a single dose of intranasal oxytocin on the physiological response, behavioural approach and avoidance response, attention, and fixation towards threatening stimuli. To conduct these meta-analyses information regarding means, standard deviations, and sample size were extracted from the included articles. Where standard errors of the mean (SE) were reported instead of standard deviations, these were converted with the following formula: $SD = SE^*\sqrt{N}$. Fourteen studies did report the data in the article or in Supplementary Materials, or reported the data in figures only. In order to acquire the required data, the corresponding authors of these papers were contacted by one of the authors. The relevant data was obtained from the following studies via personal communication: Acheson et al. (2013); Bertsch et al. (2013); Eckstein et al. (2015); Eckstein et al. (2016); Hubble et al. (2017); Kim et al., In prep; Leknes et al. (2013); Preckel et al. (2014); Striepens et al. (2012). Despite contacting corresponding authors, we were unable to gain access to the relevant data from eight studies.

In addition to healthy individuals, clinical populations included in the study consisted of people with anorexia nervosa (AN), bulimia nervosa (BN), depression, and BPD. Information regarding participants' age, dose of oxytocin (in international units), the type of task used, the