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Review article

The correlation between central and peripheral oxytocin concentrations: A systematic review and meta-analysis

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ABSTRACT

There is growing interest in the role of the oxytocin system in social cognition and behavior. Peripheral oxytocin concentrations are regularly used to approximate central concentrations in psychiatric research, however, the validity of this approach is unclear. Here we conducted a pre-registered systematic search and meta-analysis of correlations between central and peripheral oxytocin concentrations. A search of databases yielded 17 eligible studies, resulting in a total sample size of 516 participants and subjects. Overall, a positive association between central and peripheral oxytocin concentrations was revealed [$r = 0.29$, 95% CI (0.14, 0.42), $p < 0.0001$]. This association was moderated by experimental context [$Q_b(4)$, $p = 0.003$]. While no association was observed under basal conditions ($r = 0.08$, $p = 0.31$), significant associations were observed after intranasal oxytocin administration ($r = 0.66$, $p < 0.0001$), and after experimentally induced stress ($r = 0.49$, $p = 0.001$). These results indicate a coordination of central and peripheral oxytocin release after stress and after intranasal administration. Although popular, the approach of using peripheral oxytocin levels to approximate central levels under basal conditions is not supported by the present results.

1. Introduction

Oxytocin is a nine amino acid neuropeptide that acts on the widely distributed G-protein coupled oxytocin receptor in humans and almost all other vertebrate species (Horn and Swanson, 2013). Oxytocin is released both into the central nervous system (CNS) and peripheral circulation from neurosecretory cells in the paraventricular (PVN) and supraoptical (SON) nuclei of the hypothalamus, where most endogenous oxytocin is synthesized. Central and peripheral compartments of the oxytocin system are separated anatomically by the blood-brain barrier, that only in exceptional cases is appreciably permeated by oxytocin (Neumann and Landgraf, 2012).

Through central action, oxytocin is critically involved in a range of social behaviors and social cognitive functions (Guastella and MacLeod, 2012). Endogenous oxytocin levels appear to co-vary with social cognitive function at all levels of information processing in humans and other mammals, with similar observed effects after administration of exogenous oxytocin (Bartz et al., 2011). Growing clinical interest (Quintana et al., 2016a) has focused on neurodevelopmental and psychiatric conditions characterized by social cognition and behavioral impairments, such as autism spectrum disorder (ASD) (Alvares et al., 2016b; Guastella and Hickie, 2016) and schizophrenia (Shilling and Feifel, 2016), with the hope to explore the potential of oxytocin as a biomarker of these conditions, better understand their potential etiological pathways, and ultimately to ameliorate the associated social-cognitive and behavioral symptoms.

Several methodological approaches have been adopted to the study of oxytocin involvement in normal and impaired social behavior and cognition. These include the measurement of psychological or neurobiological outcomes after administration of exogenous oxytocin, and the assessment of endogenous oxytocin concentration covariance with psychological phenotypes and psychiatric disorder status. While crucial to the latter, concentrations of oxytocin have been sampled within both of these research traditions. Although the social cognitive effects of oxytocin are attributed to central mechanisms, oxytocin concentrations have typically, but not universally, been sampled in peripheral fluids such as blood plasma, saliva, and urine (McCullough et al., 2013). Consequentially, that peripheral oxytocin concentrations approximate

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central bioavailability of the neuropeptide has been a crucial assumption in research where peripheral oxytocin concentrations are correlated with psychological phenotypes or psychiatric disorder status.

Although some animal research indicates that central release from the hypothalamus and peripheral release via the posterior pituitary is coordinated (Landgraf et al., 1988; Ross et al., 2009; Wotjak et al., 1998), other research does not support this (Amico et al., 1990; Robinson and Jones, 1982). Research is also mixed in humans, with some results consistent with related levels of central and peripheral endogenous oxytocin (Carson et al., 2014), while others report no significant associations (Kagerbauer et al., 2013). After exogenous oxytocin delivered via intranasal administration in humans, one study found a significant association between cerebrospinal fluid (CSF) and blood plasma concentrations of oxytocin (Wang et al., 2013), while another found no significant association (Striepens et al., 2013). Using peripheral oxytocin concentrations to index central concentrations is clearly appealing, given the more invasive procedures required to collect centrally circulating fluids in humans. However, it is currently unclear whether and when peripheral oxytocin measures can be used to index CNS concentrations and central oxytocin bioavailability.

The present systematic review and meta-analysis synthesized studies in which central and peripheral measures of oxytocin were simultaneously sampled into a summary effect size. The strength of the summary effect size is indicative of the plausibility of peripheral oxytocin as an index for central oxytocin concentrations. As eligible studies were likely to vary in a range of contextual specifications, several potential moderator variables were considered, including experimental paradigm, oxytocin sampling location, subject species, biochemical analysis methods, year of publication, and study quality. Such differences between contexts may contribute to variance in the correlations between central and peripheral oxytocin. Thus, it is possible that peripheral oxytocin can index central oxytocin concentrations in some contexts, but not others. Together, the purpose of this study was to examine whether, and under which circumstances, peripheral oxytocin is a correlate of central oxytocin concentrations.

2. Materials and methods

The systematic search and meta-analysis was conducted in accordance with the PRISMA guidelines (Moher et al., 2009) (Supplementary Table S1) and recent recommendations for conducting correlational meta-analyses (Quintana, 2015). Prior to the execution of the systematic search and meta-analysis, the protocol for this systematic review and meta-analysis was published (Valstad et al., 2016) and pre-registered on the PROSPERO registry (CRD42015027864).

2.1. Systematic literature search and inclusion of eligible studies

A systematic literature search was performed in two iterations to retrieve studies in which oxytocin had been simultaneously sampled in fluids or tissues located in central (e.g., local extracellular fluid or CSF) or peripheral (e.g. blood plasma or saliva) regions of the body. In the first iteration, a search was performed, using Ovid, in Embase and Medline with the following combination of terms: (oxytocin) AND (concentration* OR level*) AND (plasma OR blood OR saliva* OR urin*) AND (central OR csf OR “cerebrospinal fluid”). The following constraints were applied to limit search results: the result should be (i) a full-text article or a conference abstract, (ii) written in English, that was (iii) published after 1971, when biochemical analysis of oxytocin content using enzyme immunoassay was made commercially available. Searches were conducted on April 1, 2016 and August 2, 2016, and resulted in a total of 572 studies. Out of these, 110 were relevant. A second iteration was performed in which citing articles and reference lists of included studies were examined for remaining relevant studies (Fig. 1). After retrieval, relevant studies were screened for inclusion based on the criterion that effect sizes for the correlation between central and peripheral concentrations of oxytocin must be obtainable. While 110 of the studies retrieved in the systematic search were relevant, only 17 of these satisfied this criterion.

2.2. Data extraction and management

Effect sizes and sample sizes were extracted from eligible studies. For some articles, effect sizes were stated explicitly, or directly obtainable through tables of individual values. In other articles, individual values were represented in graphs such as scatterplots, in which case a web plot digitizer (Rohatgi, 2015) was used for conversion of plots into numerical values. Since some articles contained both a scatterplot and a directly stated effect size, this plot digitizer was validated through comparing effect sizes provided by authors with plot digitizer outputs, revealing almost perfect precision (Supplementary text S2). Some articles did not provide relevant effect sizes, individual values in tables, or scatterplots. Since 15 years is a common time frame for the retention of clinical data, authors of such articles published from 2001 were contacted and asked to provide effect sizes. Articles lacking this information that were published before 2001 (n = 68), and studies performed by authors that were not able to respond to the data request (n = 25), were not included in the meta-analysis. Data were extracted from all eligible studies using a custom data extraction form (Supplementary Table S3).

2.3. Statistical analysis

Statistical analysis was performed with R statistical software version 3.2.4. (R Core Team, 2016), using the *MAc* (Del Re and Hoyt, 2012), *metafor* (Viechtbauer, 2010), and *multcomp* (Hothorn et al., 2008) R packages. The dataset and script to perform the analyses are available at https://osf.io/aj55y/

Prior to meta-analytic synthesis, raw effect sizes were transformed to Fisher’s *z* for variance stabilization (Borenstein et al., 2009). Raw effect sizes given as Spearman’s ρ were first transformed to Pearson’s *r* according to Gilpin (1993), and then transformed to Fisher’s *z* for meta-analysis. For studies reporting several effect sizes, or reporting one effect size based on repeated measures, within-study variance was estimated using a procedure described in the Supplementary text S4. A random effects model (DerSimonian and Kacker, 2007), where between-studies variance (τ^2) was estimated using a restricted maximum likelihood method, was used in the synthesis of individual effect sizes into a summary effect size. Outlier diagnostics were also performed to identify potential effect size outliers (Viechtbauer, 2010). Point estimates were converted back to Pearson’s *r* for interpretive purposes. The observed variance between studies may be due to heterogeneity (variance in the true effect sizes between studies) and within-study variance. Q, the significance of Q, and I^2 were computed in order to examine variance and heterogeneity among effect sizes of included studies. I^2 values of ~25%, ~50%, and ~75% were interpreted as low, moderate, and high, respectively (Higgins et al., 2003).

Potential moderator variables were defined *a priori* (Valstad et al., 2016). Some of the levels for moderator variables were also defined *a priori*, such as the levels *baseline condition* (lack of experimental intervention) and *intranasal administration* for the experimental paradigm moderator. Other levels of moderator variables were adjusted from pre-planned analyses *post hoc* based on the specific characteristics of included studies (for details, see Supplementary text S5). Due to the ambiguity of the concept “baseline”, an inclusive and a strict definition was adopted for sensitivity analysis, where the former was defined as lack of experimental manipulation, while the latter was defined as lack of experimental manipulation together with lack of specific context (e.g. lactation). For one of the studies (Striepens et al., 2013) effect sizes for the intranasal oxytocin (n = 11) and baseline (n = 4) conditions were not possible to disentangle, and the combined effect size was categorized in the intranasal subgroup. A sensitivity analysis for the