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Peripheral oxytocin and vasopressin: Biomarkers of psychiatric disorders? A comprehensive systematic review and preliminary meta-analysis

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ABSTRACT

A large array of studies have investigated peripheral oxytocin (OT) and vasopressin (ADH) as potential biomarkers of psychiatric disorders, with highly conflicting and heterogenous findings. We searched Web of KnowledgeSM and Scopus® for English original articles investigating OT and/or ADH levels in different biological fluids (plasma/serum, saliva, urine and cerebrospinal fluid) across several psychiatric disorders. Sixty-four studies were included. We conducted 19 preliminary meta-analyses addressing OT alterations in plasma/serum, saliva, urine and cerebrospinal fluid of 7 psychiatric disorders and ADH alterations in plasma/serum, saliva, urine and cerebrospinal fluid of 6 psychiatric disorders compared to controls. Hedge's g was used as effect size measure, together with heterogeneity analyses, test of publication biases and quality control. None of them (except serum OT in anorexia nervosa) revealed significant differences. There is no convincing evidence that peripheral ADH or OT might be reliable biomarkers in psychiatric disorders. However, the lack of significant results was associated with high methodological heterogeneity, low quality of the studies, small sample size, and scarce reliability of the methods used in previous studies, which need to be validated and standardized.

Contents

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1. Introduction

Oxytocin (hereafter OT) and vasopressin (hereafter ADH) are neuropeptides mainly synthesized in the brain's hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei (Ludwig and Leng, 2006). They are released in systemic circulation through the posterior pituitary gland, where they act as hormones regulating a range of physiological functions (Gimpl and Fahrenholz, 2001; Leng et al., 2015). They are also released in the central nervous system, acting on multiple brain regions as neuromodulators and influencing a range of neurophysiological processes and behaviours (Stoop, 2012), including feeding, anxiety, aggression, social recognition and the stress/fear response to social stimuli (Hashimoto et al., 2012).

Evidence from animal studies has demonstrated the significant role that OT and ADH play in the regulation of social behaviour and cognition (Chang and Platt, 2014). An increasing number of studies have also began to dissect the roles of OT and ADH in human social behaviour (Heinrichs et al., 2009). These neuropeptides are associated with complex social and emotional processing in healthy people which if impaired may account for some of the symptoms present in psychiatric disorders (Meyer-Lindenberg et al., 2011). Furthermore, there is also growing interest in the potential for synthetic neuropeptides in treatment of psychosis (for a comprehensive review see (Gumley et al., 2014)), autism spectrum disorders (ASD) (Thompson et al., 2006; Uzunova et al., 2015), and affective and anxiety disorders (Griebel et al., 2012).

In animals there are multiple methods that allow to reliably either assess or manipulate central OT and ADH levels and their effects on behaviour (e.g. intracerebral microdialysis (Veenema and Neumann, 2008), targeted delivery of neuropeptide agonists or antagonists (Song et al., 2014), gene knockout (Wersinger et al., 2002), and viral gene transfer (Pagani et al., 2014)). However, these are not available in humans, hence researchers have turned to peripheral assays as proxy measures. Specifically, plasma/serum (Rubin et al., 2014), saliva (Fujisawa et al., 2014), urine (Hoffman et al., 2012) or cerebrospinal fluid (CSF) (Sasayama et al., 2012) OT and ADH levels have been recently tested as putative biomarkers in ASD (Alabdali et al., 2014; Boso et al., 2007; Modahl et al., 1998), Psychosis (Elman et al., 2003; Goldman et al., 2008; Rubin et al., 2013; Walss-Bass et al., 2013), bipolar disorder (BD) (Rubin et al., 2014; Turan et al., 2013), major depressive disorder (MDD) (Goldstein et al., 2000; Ozsoy et al., 2009; Yuen et al., 2014), as well as in anxiety (Hoge et al., 2012, 2008), personality (Bertsch et al., 2013) and eating disorders (anorexia nervosa, AN and bulimia nervosa, BN) (Frank et al., 2000; Lawson et al., 2011, 2012), with highly heterogeneous and conflicting results (Al-Ayadhi, 2005; Alabdali et al., 2014; Emsley et al., 1989; Watson et al., 2007). The first aim of the present systematic review and preliminary meta-analysis was to test if the levels of these neuropeptides across different clinical samples and different biological fluids (plasma/serum, cerebrospinal fluid (CSF), urine and saliva) were consistently altered and could therefore be considered as potential reliable biomarkers for psychiatric disorders. The second aim was to investigate and address moderators and confounding factors impacting the preliminary meta-analytical estimates.

2. Methods

2.1. Selection procedures and data collection

2.1.1. Search strategies

A systematic search strategy was used to identify relevant articles. A two-step literature search was conducted by two independent researchers [GR, AS]. At a first step, the Web of Knowledge℠ database by Thomson Reuters® (including Web of Science™, BIOSIS Citation Index℠ and MEDLINE®) and Scopus® were searched. The search was extended until March 1st, 2015, including abstracts in English language only (see Supplementary materials for the electronic search code).

The second step involved the implementation of an electronic manual search of the reference lists of the retrieved articles. Articles identified through these two steps were then screened on basis of title or abstract reading. The articles surviving selection were fully downloaded (PDFs) and assessed for eligibility on the basis of full-text reading. Discrepancies were resolved through consensus with a third researcher [MR]. To achieve high quality of reporting we adopted MOOSE guidelines (Stroup et al., 2000) (see Supplementary materials).