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Saliva oxytocin measures do not reflect peripheral plasma concentrations after intranasal oxytocin administration in men

Daniel S. Quintana[a,*], Lars T. Westlye[a,b], Knut T. Smerud[c], Ramy A. Mahmoud[d], Ole A. Andreassen[a], Per G. Djupesland[e]

[a] NORMENT KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
[b] Department of Psychology, University of Oslo, Oslo, Norway
[c] Smerud Medical Research International AS, Oslo, Norway
[d] OptiNose US Inc., Yardley, PA, USA
[e] OptiNose AS, Oslo, Norway

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ABSTRACT

Oxytocin plays an important role in social behavior. Thus, there has been significant research interest for the role of the oxytocin system in several psychiatric disorders, and the potential of intranasal oxytocin administration to treat social dysfunction. Measurement of oxytocin concentrations in saliva are sometimes used to approximate peripheral levels of oxytocin; however, the validity of this approach is unclear. In this study, saliva and plasma oxytocin was assessed after two doses of Exhalation Delivery System delivered intranasal oxytocin (8 IU and 24 IU), intravenous oxytocin (1 IU) and placebo in a double-dummy, within-subjects design with men. We found that intranasal oxytocin (8 IU and 24 IU) administration increased saliva oxytocin concentrations in comparison to saliva oxytocin concentration levels after intravenous and placebo administration. Additionally, we found that saliva oxytocin concentrations were not significantly associated with plasma oxytocin concentrations after either intranasal or intravenous oxytocin administration. Altogether, we suggest that saliva oxytocin concentrations do not accurately index peripheral oxytocin after intranasal or intravenous oxytocin administration, at least in men. The data indicates that elevated oxytocin saliva levels after nasal delivery primarily reflect exogenous administered oxytocin that is cleared from the nasal cavity to the oropharynx, and is therefore a weak surrogate for peripheral blood measurements.

1. Introduction

Several psychiatric illnesses are characterized by dysfunction in social behavior, such as schizophrenia and autism. There has been considerable interest in the potential of the neuropeptide oxytocin to address social dysfunction problems in these disorders (Alvares et al., 2017; Shilling and Feifel, 2016). Preclinical research has shown that oxytocin gene knockout mice have deficits in social behavior, that are reversed with central oxytocin administration (Winslow and Insel, 2002). Following this work, research investigated peripherally circulating oxytocin concentrations, reporting reduced oxytocin in several psychiatric disorders (Hoge et al., 2008; Modahl et al., 1998) and negative associations with symptom severity (Rubin et al., 2010). Such results have contributed to increased efforts to boost oxytocin levels via intranasal oxytocin administration (Quintana et al., 2016). Intranasally administered oxytocin is thought to travel to the brain along ensheathed channels surrounding the olfactory and trigeminal nerve fibers (Lochhead and Thorne, 2012; Quintana et al., 2015a), which heavily innervate the upper and posterior regions of the nasal cavity (Doty and Bromley, 2007; Prasad and Galetta, 2007).

Although the sampling of blood plasma is a popular approach to collect peripheral oxytocin measures, which are often covaried with psychological variables [e.g., anxiety, relationship distress, attachment style (Carson et al., 2014; Strathearn et al., 2009; Taylor et al., 2010)], this is usually not practical as a trained phlebotomist is required to take blood. Blood collection phobias, which may discourage some individuals from participating in research, are also not uncommon with a lifetime prevalence of up to 5% (Bienvenu and Eaton, 1998). Saliva collection is an alternative approach to blood sampling that requires less technical expertise and circumvents needle phobia in research participants. Circulating molecules in blood plasma are thought to transfer to salivary glands via surrounding capillaries (Gröschl, 2009).

* Corresponding author.
E-mail address: daniel.quintana@medisin.uio.no (D.S. Quintana).

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The relative absence of proteins in saliva compared to blood plasma reduces the risk of assay interference (Leng and Sabatier, 2016). Given these advantages, saliva measures of oxytocin concentrations are commonly used in biobehavioral research and have also been used as a biomarker of psychiatric illness (e.g., Feldman et al., 2014; Fujisawa et al., 2014).

Despite the ease of saliva collection, there are several limitations with using saliva for peripheral oxytocin concentrations. First, the concentration of hormones in saliva is much less than blood plasma (Kaufman and Lamster, 2002), which limits comparison with the more commonly reported measure of blood plasma oxytocin. The correlation between basal saliva and plasma oxytocin concentrations is also quite modest (r values from 0.41 to 0.59; McCullough et al., 2013). Although previous studies have reported saliva oxytocin concentrations after intranasal oxytocin administration (Daughters et al., 2015; Van IJzendoorn et al., 2012; Weisman et al., 2012), little is known about the relationship between saliva and plasma oxytocin after intranasal oxytocin administration. Second, the origin of the reported increases in saliva oxytocin concentrations after intranasal oxytocin administration (e.g., Van IJzendoorn et al., 2012; Weisman et al., 2012) is not clear, especially during the first 30 min after intranasal oxytocin administration. The mucociliary clearance (Marttin et al., 1998) of intranasally delivered oxytocin from the nasal cavity to the oropharynx (also described as “trickle-down” or “drip-down” oxytocin) is a widely acknowledged limitation of saliva oxytocin measures after intranasal oxytocin administration (Daughters et al., 2015; Weisman et al., 2012). In the absence of detailed knowledge of the clearance pattern following nasal delivery of oxytocin and without radiolabeled oxytocin, it is currently not possible to separately identify trickle-down oxytocin from endogenous oxytocin or exogenous oxytocin that has been absorbed in the circulatory system and reflected in saliva via transfer from the circulatory system. An alternative approach to help distinguish endogenous oxytocin reflected in saliva from exogenous trickle-down oxytocin would be to include an intravenous (IV) oxytocin comparator, which would eliminate the confounding impact of oxytocin cleared from the nose. However, research is yet to investigate oxytocin concentrations in saliva after IV oxytocin administration.

Since nasal mucosa drug absorption is largely dependent on molecular weight, the absorption of oxytocin (1008 Da) by the nasal mucosa is relatively low (< 10%; Landgraf, 1985; McMartin et al., 1987). This suggests that much of the drug is eventually cleared from the nose. The spray deposition pattern of the delivery device, and associated clearance pattern, is likely to influence oxytocin levels in saliva after administration. Traditional spray pumps deliver approximately half of the drug to ciliated respiratory mucosa of nasal regions beyond the nasal valve (Kimbell et al., 2007; Leach et al., 2015). This fraction is rapidly cleared to the nasopharynx within 15–30 min by mucociliary clearance and sniffing (Batts et al., 1991; Lansley, 1993; Weisman et al., 2012). However, a large remainder is deposited on the sparsely ciliated transitional mucosa and non-ciliated epithelium in the anterior vestibule, from where it is slowly cleared to the nasopharynx over the course of several hours (Djupesland et al., 2013; Leach et al., 2015). Moreover, the deposition and clearance patterns may vary substantially in response to how the individual uses the device, physiological phenomena like the nasal cycle, and with pathological conditions (Djupesland et al., 2013; Leach et al., 2015; Soane et al., 2001).

A recently introduced Exhalation Delivery System (EDS) device has been shown to limit the anterior deposition to the non-ciliated mucosa, while consistently delivering a larger fraction of the administered dose to the upper posterior region of the nasal cavity (Djupesland et al., 2014; Djupesland and Skretting, 2012; Djupesland et al., 2006). Deposition to this area facilitates nose-to-brain transport as this region is heavily innervated by olfactory and trigeminal nerve fibers. Moreover, recent studies on regional clearance suggest that there is faster clearance from this region than lower regions of the posterior nasal cavity (Djupesland et al., 2014; Djupesland and Skretting, 2012; Djupesland et al., 2006). Indeed, substances administered by the EDS device tend to be absorbed or cleared to a greater extent at 30 min after administration (Djupesland et al., 2014; Djupesland and Skretting, 2012; Djupesland et al., 2006) whereas drugs administered with traditional devices would clear over longer time periods, as more of the drug is deposited on non-ciliated nasal cavity surface regions. However, the clearance of oxytocin delivered by the EDS from the nasal to oral cavity has yet to be evaluated.

In summary, there is uncertainty surrounding whether saliva oxytocin concentrations correspond to plasma oxytocin concentrations after intranasal oxytocin administration and the degree of clearance of intranasally delivered oxytocin from the nasal to oral cavity. Thus, the aim of this study was to examine the effects of EDS delivered intranasal oxytocin and IV oxytocin administration on salivary oxytocin concentrations in men, over the course of 2 h. Saliva oxytocin concentrations will also be compared with previously reported plasma concentrations from the same experiment (Quintana et al., 2015b).

2. Materials and methods

2.1. Participants

Participants were recruited through advertisements at the University of Oslo, and were eligible to participate if male, aged 18 to 35 (inclusive), and in good physical and mental health. Exclusion criteria included use of any medications within the last 14 days, history of physical or psychiatric disease, and IQ < 75. A screening visit occurred between 3 and 21 days prior to the first treatment session. The Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) and the Mini-International Neuropsychiatric Interview (Lecrubier et al., 1997) were administered to index IQ and confirm the absence of psychiatric illness, respectively. A physical examination was performed by study physicians and nurses, which included 12-lead ECG and the collection of routine blood samples, to confirm the absence of physical illness. Fifty-seven male volunteers were assessed for study eligibility, with 18 participants aged 20–30 years (M = 23.81, SD = 3.33) included (Fig. 1; Quintana et al., 2015b). Two participants withdrew after study enrollment, thus saliva oxytocin concentration data from sixteen participants were included in the analysis. This trial was approved by the Regional Committee for Medical and Health Research Ethics (REC South East) and participants provided written informed consent before they participated. The study is registered at http://clinicaltrials.gov (NCT01983514).

2.2. Study design

One of four treatments were administered in double-blind fashion using one of four randomized sequences [treatments were 8 international units (IU) intranasal oxytocin, 24 IU intranasal oxytocin, 1 IU IV oxytocin, or placebo]. A double-dummy design was adopted, whereby a nasal spray solution and IV solution was administered at every treatment session, with solution contents depending on treatment condition. The oxytocin and placebo nasal spray solutions were supplied by Sigma-Tau Industrie Farmaceutiche Riunite (Rome, Italy) to a local pharmaceutical service provider (Farma Holding, Oslo, Norway) for the filling of the nasal spray devices. The IV oxytocin (10 IU/mL; Grindeks, Riga, Latvia) and placebo formulations (0.9% sodium chloride) were added to a 0.9% sodium chloride solution. This solution was infused at a rate of 600 mL/h over a 20-minute period. The nasal spray solution was self-administered shortly after the completion of the IV infusion. Notably, the same volume of nasal spray was used for each condition so the potential trickle-down volume would be equivalent between conditions. Bottles of oxytocin contained a total of 40 IU of OT per mL, with each spray providing a 4 IU dose. Each ml of solution contained 0.2 mg of propyl parahydroxybenzoate and 0.4 mg of methyl parahydroxybenzoate. Other excipients included chlorobutanol, disodium