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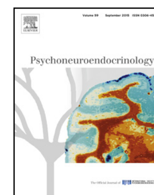

Effects of positive and negative human contacts and intranasal oxytocin on cerebrospinal fluid oxytocin

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ABSTRACT

Despite the popularity of oxytocin (OT) research for its role in social behavior, the relationship between the social environment and endogenous central OT remains poorly understood. This study investigated the effects of positive and negative human contacts and intranasal OT administration on OT concentration in the cerebrospinal fluid (CSF). The pig was used as a model, with repeated CSF sampling through a spinal catheter using a within-subject design. Positive human contact led to sustained CSF OT elevation in pigs over 120 min which outlasted the 15 min interaction. Furthermore, the frequency of positive interactions was correlated with CSF OT increase. This provides a neurophysiological basis to positive human-animal relationships, with OT preserving bonds within but also between species through interactions. Conversely, CSF OT concentration did not vary during or after negative contact with an unfamiliar person, supporting CSF OT as a biomarker of positive valence in the human-animal relationship context. Intranasal OT administration resulted in peak CSF OT within 10 min, with approximately 0.001% of the administered dose reaching the CSF. The sensitivity of the oxytocinergic system to variations in the social environment is a worthy area of investigation for its scientific and clinical implications. In particular, positive interactions result in outlasting central OT release.

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1. Introduction

The social environment is a major determinant of psychological well-being for social species (Carter, 1998). Yet, it remains challenging to assess: social interactions can be subtle and not easily detectable, are dynamic processes due to their inherent interactive nature, and lead intrinsically to subjective experiences. The hormone oxytocin (OT) could help elucidate the mechanisms of social behavior.

Oxytocin is implicated in a multitude of social behaviors amongst which are pair-bonding, attachment and social recognition (Neumann, 2009). Indeed, OT may be a biomarker for social salience (Olff et al., 2013), with its function having evolved from the filial bond to a breadth of socially-related situations (Carter, 1998; Uvnas-Moberg, 1998). Nevertheless, our understanding of the role of OT in regulating behavior has been hampered by technical and methodological difficulties.

Oxytocin's actions on behavior are hypothesized to occur mainly at central level (Landgraf and Neumann, 2004; Leng and Ludwig, 2016), but given the brain is one of the best anatomically protected organs and a health sensitive region (e.g., the blood–brain barrier), sampling central OT remains challenging. To circumvent this difficulty, a large number of studies have measured peripheral OT (in blood, saliva or urine) to interpret its role on behavior. This is despite the majority of studies reporting no consistent correlation between central and peripheral OT changes (Perlow et al., 1982; Amico et al., 1990; Kendrick et al., 1991; Winslow et al., 2003; Jokinen et al., 2012; Kagerbauer et al., 2013; Striepens et al., 2013). This is attributed to central and peripheral release patterns being governed by separate systems, and the poor ability for OT to cross the blood–brain barrier (McEwen, 2004). In addition, concerns exist with analysis of OT in plasma or serum samples without prior extraction, often against the assay kit manufacturer recommendation, or without proper validation (McCullough et al., 2013; Christensen et al., 2014). In order to overcome sampling difficulties, researchers have turned to intranasal administration of exogenous OT, with its own set of unknowns regarding the mode of action, dose and side effects (Churchland and Winkielman, 2012; Leng and Ludwig, 2016).

While awaiting for more sensitive and specific methods to quantify OT (DARPA, 2013), central OT and other neuropeptides can be measured in cerebrospinal fluid (CSF) samples (Kendrick et al., 1991; Born et al., 2002; Winslow et al., 2003; Parker et al., 2010; Jokinen et al., 2012), although the biological action of OT in CSF is

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debated (Landgraf and Neumann, 2004; Veening et al., 2010). Furthermore, intraventricular or spinal/intrathecal catheters allow for minimally-invasive, repeated sampling of CSF in live and freely-moving subjects.

Oxytocin could help unravel the proximate and ultimate causes of social behavior. However, accumulating evidence supports that OT actions are context-specific (Bartz et al., 2011; Olff et al., 2013), possibly explaining the discrepancy in the literature on OT and its (sometimes contradictorily) relationship with positive or negative social behaviors. Identifying situations or interventions that are conducive to endogenous OT release could assist practitioners in the field of mental health.

This study investigated the effects of positive and negative human contacts and intranasal OT administration on CSF OT through repeated sampling overtime in pigs. The pig is a rising biomedical model as the pig brain resembles the human brain in anatomy and development (Lind et al., 2007), while being a social species and of a size amenable to this type of study.

2. Methods

This project was approved by the University of Melbourne Ethics Committee in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

2.1. Animals

Twelve 6 weeks-old pre-pubertal female Landrace × Large White cross pigs were obtained from a commercial farm. The pigs were housed in 1.5 × 0.75 m home pen, with a feeder in front and a nipple drinker on the side of the pen. Pigs were housed adjacent to each other, with full metal sided walls and visual contact with one neighboring pig through a wire mesh wall at the back of the pen. They were provided with balls for environmental enrichment (Pawzzle Ball Dog Toy, Hueter Toledo Inc., Bellevue, OH, USA). Pigs were fed ad libitum a commercial diet mix. Caretakers interacted with each pig through vocal and gentle physical touches at least 5 min twice daily for 2 weeks prior to the tests to ensure that they were used to human presence and handling. All pigs were moved individually three times to the 1 × 1 m testing pen located 15 m away from their home pen in a different room to familiarize them with the testing environment.

2.2. Surgical procedures for spinal catheter placement

After fasting overnight, each pig was sedated with an intramuscular injection of an anesthetic agent mixture (Alfaxalone 1 mg/kg, ketamine 5 mg/kg, medetomidine 20 mg/kg, hydromorphone 0.1 mg/kg), and catheterized through the auricular vein. After endotracheal intubation, the pig was connected to an anesthesia machine via a rebreathing system and allowed to breathe 100% oxygen at 1 L/min. Anesthesia was maintained using alfaxalone at a constant infusion rate (0.05–0.2 mg/kg) for the remaining of the procedure to ensure a steady state of anesthesia. Lacrilube was administered to the eyes to prevent drying of the cornea. The pig was allowed to breathe spontaneously throughout the experiment.

All materials and procedures used during the surgery procedure were kept aseptic, with the area of surgery cleaned with a chlorhexidine and salvon solution and rinsed with 70% ethanol. The procedure consisted of injecting 3 mL of lignocaine subcutaneously before making a small incision in the skin of 0.5 cm with the width of the scalpel blade to ease the crossing of the needle through the pig's tough skin. A spinal needle (B-Braun® SPINOCAN Spinal needle, 16 Ga × 8.9 cm, B-Braun Medical, Boulogne Billancourt, France) was inserted into the spinal subarachnoid space by lumbar puncture through the lumbar 4 and 5 interspace, the needle advancing until the dura mater was pierced. Placement was verified by dripping of CSF through positive pressure. Once the correct placement was verified, a spinal catheter (B-Braun® PERIFIX Epidural catheter set, 18 Ga × 100 cm, B-Braun Medical, Boulogne Billancourt, France) was fitted to obtain from 2 to 5 cm of penetration inside the subarachnoid space and secured using a tape externally glued to the outer edge of the skin. Correct catheter placement was checked by fluoroscopy and sutured to the skin to ensure that the catheters did not slip out. The external part of the catheter was kept in a small pouch glue on the back of the pig to ensure that they could not damage or remove the catheter and maintained the catheter clean at all times. Each pig was given one week to recover before the start of the test, and catheters were flushed daily throughout the experiment with a 0.9% sterile saline solution.

Twelve pigs underwent surgery, but only 5 pigs had long-lasting functional catheters. Each pig with a functional catheter was subjected individually to the different tests every other day, in the morning, in the following order.

2.3. Positive and negative human contacts

Five pigs underwent the positive human contact test and four of these pigs underwent the negative human contact test to assess the effects of the nature of human contacts on the pig's CSF OT concentration.

First, the effect of positive human contact was tested. The caretaker stood in the corner of the testing pen. The pig was moved to the testing room by another handler and placed in the testing pen for 15 min. If the pig approached the caretaker, the caretaker interacted with the pig in a gentle way, petting the pig on the head and neck or talking softly, without voluntarily encouraging the pig to approach. The caretaker was used as a familiar person with whom the pig had a previous positive experience. The handler entered the room 5 and 15 min after the start of the test for CSF sampling. At the end of the 15 min, the pig was moved back to her home pen, and sampled 30, 60 and 120 min after the start of the test.

The effect of negative human contact was tested two days later. The order of the two tests was chosen because there were higher chances to have carry-over effect from negative to positive contacts than the reverse, given that the pigs only experienced positive human contact after arriving in the experimental settings. An unfamiliar human stood in the corner of the testing pen. The pig was moved to the testing pen in the same way as for the positive human contact test for 15 min. However, if the pig approached the unfamiliar human, the human interacted with the pig in a negative way by delivering a quick and firm slap to the pig (not forceful or exaggerated, but strong enough to force the pig to move away) or shout at her to simulate a mild negative interaction. The person chosen was an unfamiliar person so as to avoid the pig having previous knowledge about the way this person would interact. The sampling of CSF occurred in an identical manner to the positive human contact test.

2.4. Intranasal saline and oxytocin administration

Three pigs underwent the intranasal saline and OT administrations. This test assessed the time required for intranasal OT administration to influence lumbar CSF OT, and the magnitude of OT concentration change. The experimental pig remained in her home pen and was first administered intranasally 0.5 mL of 0.9% saline as a control, with a half dose in each nostril, using a Mucosal Atomizer Device (MAD 300, Wolfe Tory Medical Inc., Salt Lake City, UT, USA) connected to a 1 mL syringe according to a procedure used previously for OT intranasal administration in pigs (Rault et al., 2013). Cerebrospinal fluid samples were taken prior to administration, 60 and 120 min after saline administration. The following day, the pig was administered an intranasal dose of 24

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