Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Research Report

Intranasal oxytocin effects on social cognition: A critique

Simon L. Evans[a,1], Olga Dal Monte[b,c,1], Pamela Noble[b], Bruno B. Averbeck[b,*]

[a]School of Psychology, University of Sussex, Brighton, East Sussex BN1 9QG, United Kingdom
[b]Laboratory of Neuropsychology, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA
[c]Department of Neuropsychology, University of Turin, Turin, Italy

ARTICLE INFO

Article history:
Accepted 7 November 2013
Available online 14 November 2013

Keywords:
Oxytocin
Intranasal administration
CSF
Social stimuli
Pro-social neuropeptide
Anxiety
Social cognition

ABSTRACT

The last decade has seen a large number of published findings supporting the hypothesis that intranasally delivered oxytocin (OT) can enhance the processing of social stimuli and regulate social emotion-related behaviors such as trust, memory, fidelity, and anxiety. The use of nasal spray for administering OT in behavioral research has become a standard method, but many questions still exist regarding its action. OT is a peptide that cannot cross the blood–brain barrier, and it has yet to be shown that it does indeed reach the brain when delivered intranasally. Given the evidence, it seems highly likely that OT does affect behavior when delivered as a nasal spray. These effects may be driven by at least three possible mechanisms. First, the intranasally delivered OT may diffuse directly into the CNS where it directly engages OT receptors. Second, the intranasally delivered OT may trigger increased central release via an indirect peripheral mechanism. And third, the indirect peripheral effects may directly lead to behavioral effects via some mechanism other than increased central release. Although intranasally delivered OT likely affects behavior, there are conflicting reports as to the exact nature of those behavioral changes: some studies suggest that OT effects are not always "pro-social" and others suggest effects on social behaviors are due to a more general anxiolytic effect. In this critique, we draw from work in healthy human populations and the animal literature to review the mechanistic aspects of intranasal OT delivery, and to discuss intranasal OT effects on social cognition and behavior. We conclude that future work should control carefully for anxiolytic and gender effects, which could underlie inconsistencies in the existing literature.

This article is part of a Special Issue entitled Oxytocin and Social Behav.

Published by Elsevier B.V.

1. Introduction

Oxytocin (OT) is a peptide that has numerous functions in the body, both peripherally as a hormone and centrally as a neurotransmitter, and OT-like peptides can be found in nearly all vertebrate species (Gimple and Farenholtz, 2001). Peripheral functions are wide in range. OT has a well-established role in reproductive function (Corona et al., 2012; Courtois et al., 2013)

*Corresponding author. Fax: +1 301 402 0046.
E-mail addresses: bruno.averbeck@nih.gov, averbeckbb@mail.nih.gov (B.B. Averbeck).
[1]S.L.E. and O.D.M. contributed equally and are co-first authors.

0006-8993/$ - see front matter Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.brainres.2013.11.008

and in parturition and lactation in females (Carson et al., 2013; Gimple and Farenholtz, 2001). Synthetic OT has been used to assist in childbirth for decades. In addition, OT receptors are located in visceral organs such as kidneys and pancreas, as well as in the heart, fat cells, and adrenal glands (Gimple and Farenholtz, 2001), and OT has been found to be involved in the regulation of water balance, bone density, and appetite (Carson et al., 2013).

In contrast, it has been suggested that OT effects in the central nervous system (CNS) might be more specific, with OT playing an important role in modulating social behaviors and the processing of social stimuli. Whether these behavioral changes are modulated by OT in system-specific ways or due to more general effects are, however, unknown. The study of central effects of OT has been carried out in animal models and humans using different delivery methods: in animals both central and peripheral administration has been used, while in humans studies investigating the effects of exogenous OT typically use intranasal spray for delivery, with few exceptions (Hollander et al., 2003). How or if the OT enters the brain using this method is, however, still unknown. The purpose of this critique is twofold. We firstly discuss the potential mechanisms by which OT could enter the brain, and weigh the evidence from work in animals. Implications for human studies using intranasal OT are discussed. We then provide an overview of intranasal OT effects on social cognition in healthy humans, and explore whether OT is genuinely a neuropeptide with specifically "pro-social" effects. We incorporate findings published since other recent reviews on this topic (Bartz et al., 2011; Guastella et al., 2013; MacDonald et al., 2011), identify potential confounds that could underlie current inconsistencies in the literature, and provide suggestions as to how these could be resolved. In tying together both the mechanistic and behavioral aspects of intranasal OT delivery, we provide a summary several issues as a guide for future research.

2. Intranasal delivery: mechanisms

The OT peptide is composed of nine amino acids and is produced in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus in mammals. OT is released peripherally primarily from the neurohypophysis by exocytosis (Carson et al., 2013; Viero et al., 2010). Since OT is a relatively large, hydrophilic molecule, blood–brain penetration is too poor to cause any measurable effects on central systems (McEwen, 2004), so peripheral OT likely re-enters the brain in negligible amounts. Instead, OT is released directly in the CNS by OT neurons that project to numerous brain regions from the PVN, separate from those that go to the pituitary (Ross and Young, 2009; Veening et al., 2010).

OT receptors are widely distributed through many brain areas in rat, including the spinal cord, brainstem, hypothalamus, amygdala, and nucleus accumbens (Ross and Young, 2009). While localization of OT receptors has yet to be definitively mapped in primates and humans (Toloczko et al., 1997), efforts are being made to develop a radioligand that will bind with high specificity to human OT receptors (Smith et al., 2012). Distribution patterns of OT receptors across brain areas are highly species dependent (Insel and Shapiro, 1992; Young et al., 1996), and binding sites are up-regulated in specific areas in response to peripheral (such as pregnancy) or environmental (such as social cooperation) cues (Viero et al., 2010). Many OT neuron axonal projections run close to the ventricles, which may allow for release of OT into the ventricles for communication across numerous OT-receptive brain areas via the cerebrospinal fluid (CSF) (Veening et al., 2010). It has been proposed that this global communication process through CSF within the CNS is what may allow for the necessary simultaneous changes in the numerous neural mechanisms involved in rapid behavioral adaptation to environmental stimuli (Veening et al., 2010).

2.1. *CSF versus plasma*

The relationship between peripheral (plasma) and central (CSF) OT levels is complex. Studies in humans are typically restricted to peripheral OT assessments due to the risks associated with invasive CSF collection procedures (Carter, 2007; Challinor et al., 1994; Domes et al., 2010; Modahl et al., 1998; Parker et al., 2010). Studies that use measures in plasma to track changes in OT levels after nasal administration in humans have found significant increases in OT levels from baseline at 30 min (Gossen et al., 2012), 45 min (Domes et al., 2010), and over the course of 1 h (Burri et al., 2008). Furthermore, a number of human studies have reported correlations between peripheral levels of endogenous OT and behavior. High levels of plasma OT have been associated with trust and trustworthiness (Zak et al., 2005, 2007), positive physical contact with a partner (Grewen et al., 2005), and lower levels of anxiety in patients with depression (Scantamburlo et al., 2007). By contrast, low peripheral levels of OT have been found in patients with depression (Cyranowski et al., 2008), schizophrenia, (Goldman et al., 2008; Keri et al., 2009) and autism spectrum disorders (Green et al., 2001).

However, there are numerous animal studies that show no correlation between plasma and CSF levels of OT in response to a variety of manipulations, ranging from hormone administration to environmental cues (Amico et al., 1990; Rosenblum et al., 2002; Seckl and Lightman, 1987; Veening et al., 2010; Winslow et al., 2003). Winslow et al. (2003) reported significant differences in endogenous CSF OT levels between nursery and mother reared rhesus monkeys over a period of development, but no difference in plasma OT between the groups, and no correlation between CSF and plasma OT. Because OT cannot cross the blood–brain barrier (BBB), central and peripheral OT systems may be independently regulated, thus peripheral and central effects of OT are thought to be coordinated through its common release as a result of collateral axons in the pituitary and nucleus accumbens (Ross and Young, 2009). It may be that correlations cannot be detected due to temporal differences in responses between peripheral and central systems (Neumann et al., 2013). Bioavailability differs significantly in plasma versus CSF; OT is broken down within 2 min in plasma, while it lasts for up to a half an hour in CSF due to a lack of hydrolyzing enzymes (Jones and Robinson, 1982; Mens et al., 1983; Robinson et al., 1982; Robinson and Coombes, 1993; Veening et al., 2010; Viero et al., 2010).