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LETTER TO THE EDITOR

Oxytocin administration affects the production of multiple hormones

Studies utilizing Oxytocin (OT) nasal spray should look at the interaction between OT and other hormones in order to better understand its role in the regulation of complex social behaviors and social cognitions. Additionally, peripheral OT may used as an index for exogenous OT bio-availability.

Guastella et al. (2013) recently published in this journal a much needed paper calling to standardize the use and report of OT nasal administration protocols, as well as to inform readers on the different bodily routes through which OT manipulation may exert its reported effects. Following their paper, we wish to underscore two aspects that are central to the field of OT administration research and may shed further light on the effects of exogenous OT on human behavior.

First, we suggest that research investigating OT effects should consider a possible cross-talk or interplay between the OT system and other hormones in the interpretation of the findings. A more thorough understanding of the relationships between exogenous OT and key brain hormones and modulators is central to research on the neurobiological correlates of human social engagement. For instance, in a recent study conducted at our lab (Weisman et al., 2012b), we found that intranasal OT administration increased salivary levels of the structurally-related neuropeptide, arginine vasopressin (AVP), in both male and female subjects during the first hour following manipulation. However, unlike the findings for salivary OT (Weisman et al., 2012a) — which increased over four consecutive hours — AVP increased only during the first post-administration hour. In a second study (Weisman et al., submitted for publication), we found that OT administration modulated fathers' salivary testosterone (T) levels. We also found correlations between baseline levels of OT, AVP, T, and cortisol (CT) and that the inter-relatedness between these hormones defined the individual's response to OT administration. These findings add to the accumulating evidence indicating that OT administration modulates endogenous levels of several other hormones, such as progesterone, epinephrine, and alpha-amylase, in humans. Another angle to this argument is that OT effects may vary according to receptor distributions in key brain areas and thus, specific brain networks may shape the effects of OT administration on the individual's behavior. Overall, these data accord with the recent notion that OT effects are nuanced, non-uniform, and depend on a host of biological and psychological factors.

Second, we would like to highlight the possibility that endogenous levels of OT in blood, saliva (and to a lesser extent in urine) may be used as biomarkers of central activity, albeit with caution and further research. Recent studies conducted at two different labs, including ours, showed that OT administration substantially increased salivary OT levels measured repeatedly across four (Weisman et al., 2012a) and seven hours (van Ijzendoorn et al., 2012), and that OT effects on salivary levels were observed already 15 min after administration. Notwithstanding the complexities of the central-peripheral coordination of the OT system, we believe that further study on the effects of OT administration on peripheral expression of multiple hormones may pave the way to better understanding how OT administration impacts human social behavior.

Contributors

Authors OW and RF contributed to and have approved the manuscript.

Conflict of interest

Drs. Weisman and Feldman have no conflict of interest to disclose.

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LETTER TO THE EDITOR

Unitary hormonal models, peripheral markers, and evaluation of response to drug: A response to Weisman and Feldman

There is growing recognition of the complexity in studying cognitive, behavioral, and neural effects of oxytocin (OT) administration in humans. We recently emphasized the importance of standardization of experimental methodologies assessing social cognition (Guastella and MacLeod, 2012) and delivery of peptide nasal spray (Guastella et al., in press) in such investigations. This is partly in response to a growing number of reported and inconsistent individual differences and contextual factors believed to moderate response, combined with a lack of consideration for factors associated with experimental designs.

Weisman and Feldman (2013) have thoughtfully placed debate about unitary hormonal explanations and argued for the study of interplay between hormonal and neurochemical systems (e.g. Bos et al., 2012; Goodson, 2013). In addition to what occurs subsequent to OT release, animal studies reveal a remarkable lack of receptor selectivity amongst OT and vasopressin agonists and antagonists, as well as interspecies differences in selectivity (Manning et al., 2012). Receptor selectivity may be further lost when higher doses of drug are employed (Manning et al., 2012). As Insel (2010) noted, the efficacy of peptide administration is also likely to be moderated by genetic variants in receptor expression. Elevations or suppression of hormones may, therefore, not only be triggered by increases in OT levels (exogenous or endogenous), but also via receptor cross-reactivity of agonists/antagonists and individual differences in receptor expression.

To assess interplay between hormonal systems, Weisman and Feldman, 2013 argued for the use of biological markers of hormone levels in blood, saliva, and urine. We support their view but also note that standardization of measurement and clarification of mechanism is needed. First, the field needs to resolve discrepancies around reliable and sensitive methods (bioassays, procedures) for conducting analyses and agree on 'gold standard' procedures across laboratories. Accessibility for researchers to then employ these techniques is paramount. Second, synchrony between peripheral and central hormonal systems is not fully understood. This is important considering OT receptors (and other receptors types) are distributed widely throughout both central and peripheral nervous systems (Gimpl and Fahrenholz, 2001). Integrating measures within a battery of assessments likely to be associated with alterations of central systems and therapeutic response, including cognitive (social cognition), behavioral (e.g., trust), and physiological (eye gaze; heart rate variability) assessments, will enhance the ability to detect reliably initial responses that are predictive of a longer-term benefit of nasal spray administration in humans.

Lastly, to address some uncertainty, the development of radioligands for use in OT receptor mapping and occupancy studies in the human body by Positron Emission Tomography (Smith et al., 2012, 2013) remains a priority. Whole body dynamic scans following OT administration would allow the visualization and quantification of the distributions pathways of OT, as discussed in our review. Differential distribution could be linked to proposed response markers and other individual difference factors that modulate response. As this discussion highlights, the complexity of conducting translational research in humans requires strong focus on methodological rigor in the operationalization and assessment of constructs and effective and standardized drug delivery procedures.

Contributors

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Conflict of interest

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