Intranasal oxytocin mechanisms can be better understood but its effects on social cognition and behavior are not to be sniffed at

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Keywords: oxytocin, intranasal, social cognition, social behavior

Word count: 983 words

To the Editor:

The administration of intranasal oxytocin (IN-OT) has demonstrated a wide range of effects on social behavior and cognition, which has led to its proposed use as a treatment for psychiatric disorders characterized by social cognition deficits. Recently, Leng and Ludwig (1) raised a number of important issues in regards to IN-OT research in their provocatively titled review. We wholeheartedly agree with the authors' sentiments that the mechanisms underlying IN-OT are poorly understood (2). However, the authors appear to be making the case that the behavioral effects of OT are suspect because the specific mechanisms of IN-OT's effect on social behavior and cognition are not well known. We would like to remark on some aspects of this review and highlight recent IN-OT work that provides much needed dose-response data controlling for peripheral effects.

The ability of IN-OT to alter behavior, cognition, and related neurophysiology in humans is well established with several recent meta-analyses supporting positive effects of IN-OT on facial emotion recognition (3) modulation of neurophysiological responses to social stimuli (4), and symptom improvement in psychiatric illness (5). In contrast to the authors' assertion of widespread publication bias in the IN-OT literature, these meta-analyses revealed no evidence of publication bias. Relatedly, we were also surprised to read one of our studies (6) cited as evidence that IN-OT has no effect on patients with schizophrenia or healthy volunteers. In fact, our study found large effects of IN-OT on high-level social cognition in patients with schizophrenia and partially replicated previous findings in healthy individuals. This particular effect of IN-OT on high-level social cognition in schizophrenia has been found independently by other groups (7) and remains significant after doubling our sample

size (n = 54 individuals with schizophrenia; Woolley, unpublished data). The partial replication of IN-OT effects in healthy individuals may be due to the higher dosage of OT (40IU) used in this study compared to previous studies. In sum, while there have certainly been negative IN-OT studies, particularly related to trust, it would be premature to disregard past evidence supporting the effectiveness of IN-OT.

The authors raise the question of whether the large IN-OT dosages used in most studies can deliver enough OT to the brain. Although IN-OT administration leads to only physiologically modest rises in CSF OT measures, these increases may still be functionally relevant (8), consistent with the observed changes in cognition, behavior, and neural responses after IN-OT (3-5). The precise characterization of IN-OT transport is certainly important from a mechanistic perspective as this can guide and improve future work (2). However, the previously demonstrated social-cognitive effectiveness of IN-OT should not be dismissed simply because these nose-to-brain delivery processes are not yet well understood in humans. Relatedly, the authors also call attention to the critical step of sample extraction when quantifying plasma OT. However, none of the seven studies cited for not extracting OT actually administered IN-OT to observe its effects; these studies only investigated the behavioral or diagnostic correlates of peripheral OT. These analytic issues notwithstanding, questionable methodology in studies investigating behavioral correlates of OT measures are again not strictly germane to the question of whether IN-OT is effective in modulating social cognition and behavior. Primary outcome measures are typically improvements in behavior or cognition, not the levels of CSF or plasma concentrations or whether plasma concentration can be used as a proxy for CSF levels, which are usually secondary considerations to better understand underlying processes.

To advance the field, IN-OT research needs to pivot to understanding "how", "where", and for "whom" it works, rather than just simply adding to the growing catalogue of "what" effect this neuropeptide has on cognition and behavior. Working towards this goal, we recently compared two doses of IN-OT (8IU and 24IU) with intravenously (IV) administered OT (1IU delivered over 20 minutes; this treatment regime provided equivalent peripheral OT concentrations to IN-OT) and placebo on social cognition in a 4-way, within-subject, double-dummy, crossover single administration trial in sixteen healthy participants (9). This study design provided the opportunity to control for peripheral effects and compare central vs. peripherally targeted OT delivery to the brain. We observed a main effect of treatment on anger ratings of ambiguous faces, with follow-up comparisons revealing deceased anger ratings after 8IU IN-OT (but not after 24IU IN-OT) compared to placebo treatment, despite comparable concentrations of peripheral OT after all three active treatments. These data are consistent with centrally mediated effects and raise the intriguing possibility that a lower IN-OT dosage may in fact be more efficacious for the modulation of social cognition, perhaps due to V1 vasopressin receptor cross-reactivity at higher OT dosages. Additionally, evidence of a social behavioral effect after 8IU IN-OT, but not IV OT, suggests that activation of peripheral targets may not influence social cognition, at least in healthy individuals.

The behavioral and cognitive effects of IN-OT that may translate into future treatments are clear. A poor understanding of how IN-OT exerts its effects does not mean that IN-OT may not hold promise as a treatment for psychiatric symptoms. At present there are no approved psychopharmacological therapies to redress deficits in social cognition and behavior. Repurposing an "old" therapeutic for new indications provides tremendous savings in resources and time (10). Thus, by prematurely

dismissing IN-OT for psychiatric treatment simply because the mechanism is not completely understood, the field may lose the opportunity to fully realize a novel psychiatric treatment at a fraction of the cost typically required for drug development. Furthermore, the exact mechanisms of action for many widely used and efficacious psychopharmacological interventions remain unclear, including selective serotonin reuptake inhibitors.

In conclusion, we hope such discussion continues to stimulate a better understanding of OT's mechanisms in an effort to understand and improve its observed effects on social behavior and cognition. While IN-OT certainly is not a panacea for all psychiatric diseases, we should not adopt the other extreme and disregard its effects for lack of comprehensive understanding.

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