Letter to the Editor

“Shedding light on a dark question”: Peripheral oxytocin signalling and neurobehavioral responses to intranasal oxytocin in humans

Dear Editor,

We read with great interest the original research of Quintana et al. (2016) published in Psychoneuroendocrinology (volume 69, p180–188). In this study, the authors addressed two pressing questions in the field: how dose and route of administration of exogenous oxytocin modulates neural responses during facial emotion recognition (one of the experimental paradigms that has produced the most reproducible findings in oxytocin research).

We are still far from understanding the exact mechanisms through which the transnasal administration of oxytocin affects brain function and behavior. Although some models have been proposed to explain neuropeptide diffusion from the nasal cavity to the central nervous system (CNS), there is a scarcity of knowledge about the exact mechanisms underlying nose-to-brain oxytocin transportation, the potential role of peripheral oxytocin effects, or the effects of dose. These questions, in addition to uncertainty over the origin (i.e., endogenous vs. exogenous) of observed increases in oxytocin concentration in the cerebrospinal fluid (CSF) after intranasal administration, have prompted skepticism regarding the use of intranasal oxytocin in human research.

Such concerns stem partly from the observation that while the intranasal administration of oxytocin may achieve modest increases in CSF concentration, it produces a large and prolonged increase in peripherally circulating oxytocin (to levels far above those needed for lactation or labor) (Striepens et al., 2013; Modi et al., 2014; Dal Monte et al., 2014). This observation has prompted the idea that the observed CNS effects following intranasal oxytocin administration are indirect, i.e. that they result from the peripheral activation of oxytocin receptors (or of vasopressin receptors activated at high concentrations of oxytocin), and that the consequent small increases in CSF oxytocin levels are physiologically irrelevant (Evans et al., 2014). Unfortunately, proper dose-response studies and studies controlling for peripheral effects by blocking peripheral actions with antagonists are still lacking to help disentangle these issues. (Evans et al., 2014).

Quintana et al. (2016), nevertheless, addressed some of these questions by showing that the intravenous administration of oxytocin in a dose that achieved a comparable rise in blood oxytocin levels to that produced by the intranasal administration did not modulate the response of amygdala during emotional facial recognition. This study provides important evidence supporting the idea that intranasally administered oxytocin may modulate brain activity directly.

Further studies to clarify the precise mechanisms through which the intranasal administration of oxytocin may affect brain function and behavior and understand its pharmacodynamics (Paloyelis et al., 2016), will increase the methodological quality of oxytocin research and, in our opinion, are urgently needed. Importantly, Quintana et al. provide a glimpse of hope that current limitations should not hinder ongoing investigations using intranasal oxytocin as a tool for unravelling its role in social cognition or exploring its potential as a neuropsychiatric treatment.

Conflict of interests

The authors declare no conflict of interests.

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References


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