Oxytocin: pain relief in skin

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The hypothalamic neuropeptide oxytocin attracts the attention of both the neuroscientific community and the general public, especially because of its prosocial effects. In the brain, this neuropeptide is synthesized in neurons exclusively located within the hypothalamic nuclei. Magnocellular neurons compose the larger population of oxytocinergic neurons, project to the posterior pituitary lobe and, from there, release oxytocin into the blood stream. Simultaneously, these neurons project to extrahypothalamic forebrain areas such as the amygdala, hippocampus, and cerebral cortex.[11] A smaller population of parvocellular oxytocinergic neurons release oxytocin in the brainstem and spinal cord but not in the blood flow. Thus, through synchronized release into the blood and the central nervous system (CNS), oxytocin is able to exert both central and peripheral actions to modulate a variety of social and nonsocial behaviors, including nociception and pain.[12,17]

During the past years, our current understanding of how oxytocin modulates brain circuits to attenuate nociception and pain perception has been under intense scrutiny.[6,8,10] Indeed, oxytocin acts in CNS regions of the hierarchically organized pain matrix, among which are several cortical regions, amygdala, raphe nucleus, periaqueductal gray, and spinal cord. Most recently, it was shown that a minor population of parvocellular oxytocin neurons exert a dual action, through systemic and central mechanisms (**Fig. 1**), to inhibit the wide-dynamic-range sensory neurons in the spinal cord.[4] By contrast, the precise peripheral sites of action and the mechanisms involved in peripheral oxytocin-mediated analgesia are still unclear. Indeed, only a few studies have reported that afferent neurons of the dorsal root ganglia (DRG) express oxytocin receptors, predominantly in nonpeptidergic C-fiber cell bodies,[16,25] suggesting that peripheral oxytocin can penetrate the DRG and directly act at the peripheral level of the so called pain matrix.[4]

In this issue of *PAIN*, González-Hernández et al.[7] propose a new site for physiologically relevant oxytocin modulation of nociception: the peripheral nociceptive terminal axons in skin. A single subcutaneous administration of oxytocin per se induced a long-lasting (up to 100 minutes) inhibition of nociceptive integration in the spinal cord, as shown through wide-dynamic-range neuron recordings. In a formalin pain model, oxytocin inhibits flinching behavior through peripheral oxytocin receptor activation. Finally, an immunosignal for oxytocin receptor was detected in the nociceptive-specific terminals of the superficial skin layers. Altogether, this combination of approaches and findings indicates that activation of skin-located oxytocin receptor contributes to oxytocin-mediated analgesia.

In line with numerous indications that oxytocin can act at peripheral organs, such as the uterus, mammary gland, and the cardiovascular and digestive systems,[2,5,9,24,26] the present paper is the first report demonstrating physiological expression of oxytocin receptors in peripheral nociceptive fibers of the largest peripheral organ: skin. Although interpretation of anatomical data of the paper remains difficult because of the general problem with detection limit of oxytocin receptors by available antibodies, the fact that nociceptive fibers can be directly affected by oxytocin raises numerous questions and, hence, stimulates prospective studies.

It is well known that peripheral organs are capable of locally producing oxytocin synthesis, which can exert each of two effects, auto and paracrine.[5] In respect to skin, the keratinocytes are likely candidates for local synthesis of oxytocin.[2] Given that self-soothing is an usual and simple way for low-intensity pain relief,[20] one can propose that tactile stimulation induces keratinocytes-mediated oxytocin release,[2] thus leading to a skin-localized oxytocin receptor activation-mediated analgesia. This is particularly interesting because stimulation of nociceptive fibers, the ones described by González-Hernández et al. as expressing oxytocin receptor, is a proposed mechanism for touch-induced oxytocin release.[22] This opens the possibility of a strictly peripheral, skin-based, closed loop concept of oxytocin-induced analgesia (**Fig. 1**). However, it is well documented that painful states raise plasma oxytocin concentration.[5,10,14] Although brain and peripheral releases of oxytocin cannot be distinguished in these studies, both blood and skin oxytocin could directly act on skin terminals of nociceptors. Altogether, this reminds us that oxytocin is not only a neuropeptide but also a peripheral hormone and highlights that future investigations are requested to discriminate the source of oxytocin dominantly acting at the level of the skin.

Another intriguing point is the mechanism involved in oxytocin-mediated analgesia at the level of axonal terminals. Although it was proposed that oxytocin receptors can be allocated in presynaptic sites of serotoninergic neurons,[3] it is still unclear which cellular cascades can be initiated at sensory terminals to inhibit the activity of DRG neurons. Given that the oxytocin receptor can be coupled with either Gi or Gq protein,[1] one can hypothesize that its activation prevents the overstimulation of nociceptive fibers by analogy to the proposed shunt-like mechanism for classical neurotransmitters.[18] However, this is still an open question and understanding the precise mechanism
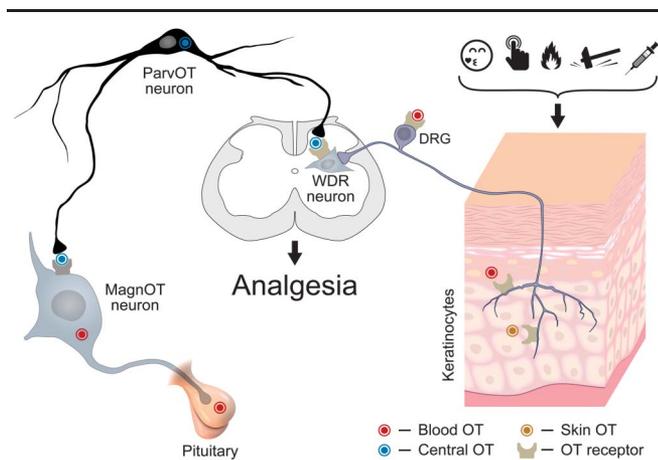
Figure 1. Schema depicts the proposed mechanism for the oxytocin-mediated peripheral analgesia. Oxytocin may acts through a 3-way path: spinal cord central release, to directly inhibit WDR neuron activity; blood release, through pituitary, to inhibit either the cell body or peripheral nociceptive fibers of DRG neurons; and skin release, to directly inhibit the excitation of nociceptive fibers. These mechanisms may be induced by skin-based stimulation such as skin-to-skin interaction, gentle touch, or nociceptive stimulation. WDR: wide-dynamic-range; DRG: dorsal root ganglia.

involved would be a major breakthrough in the neuropeptides domain.

During the past decade, several clinical trials on intranasal oxytocin treatment of human patients afflicted with social deficits have been successfully accomplished, opening a road for implementation of this neuropeptide as a novel drug in both psychiatry and pain-specialized clinics, especially for chronic pain.[19,23] Given that the current study only addresses acute pain, will peripheral administration of oxytocin have an analgesic effect on other types of pains? Particularly, the most concerning pains faced in human clinics still lack efficient medication—in adults: neuropathic pains[21]; in infants suffering anticancer treatments: oral mucosities.[15] As the latter originate from inflamed mucous membranes, is there a possibility for topical application of an oxytocin-like molecule to ease those pains? On a different but similar line, application of such an oxytocin skin release mechanism could enhance the understanding, and subsequent more widespread recognition, of the beneficial analgesia induced by skin-to-skin interaction between an infant and his/her mother.[13]

In conclusion, González-Hernández et al.[7] provided a comprehensive set of data which bring a new level of understanding of the complexity of oxytocin-mediated analgesia by interrogating the relationship between the CNS and the periphery during pain. This excellent work brings up a putative 3-way oxytocin–mediated analgesia and raises numerous basic and clinically relevant questions, paving the way to interesting discussions and future research.

Conflict of interest statement

The authors have no conflict of interest to declare.

Acknowledgements

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