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BEHAVIOURAL NEUROSCIENCE

Taking axonal delivery of oxytocin

Oxytocin affects various social behaviours by acting on forebrain regions including the amygdala, which has a key role in mediating fear responses. Nevertheless, how this neuropeptide reaches these regions has been a matter of debate. Now, Knobloch, Charlet *et al.* show that axons of oxytocin-positive hypothalamic neurons pervade many forebrain areas and that axonal oxytocin release from such neurons in the central amygdala (CEA) reduces fear responses.

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To investigate how oxytocin reaches the forebrain, the authors first created a recombinant adeno-associated virus in which the fluorescent marker Venus was placed under the control of an oxytocin promoter. They then infected the hypothalamic paraventricular, supraoptic and accessory magnocellular nuclei (the main sites of oxytocin production) of rats with this virus and examined the distribution of this marker.

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Interestingly, Venus-positive fibres were found to extend to various forebrain structures, including the CEA, and to morphologically resemble axons. Expression of fluorescently tagged axonal and synaptic markers in oxytocin-positive neurons confirmed the axonal nature of these fibres and revealed contacts between these neurons and dendrites in the lateral subdivision of the CEA (CEL).

These findings suggest that long-range hypothalamic axonal projections deliver oxytocin into the CEA and other forebrain regions. To provide further evidence for this assertion, the authors adopted an optogenetic approach and expressed blue-light-sensitive channelrhodopsin 2 (ChR2) in oxytocin-positive hypothalamic neurons in rats. In horizontal CEA slices, blue light induced a rise in action potential frequency in CEL neurons. These neurons release GABA onto neurons in the medial subdivision of the CEA (CEM), and a rise in the frequency of inhibitory postsynaptic currents (IPSCs) in CEM neurons could also be seen with exposure to blue light. The increases in CEL activity and CEM IPSCs were largely blocked by an oxytocin receptor antagonist, indicating that oxytocin release from hypothalamic axons activates CEL neurons.

The authors next examined the effects of this hypothalamic axonal release of oxytocin on behaviour. They expressed ChR2 in oxytocin-positive hypothalamic neurons in female rats that had cannulae inserted into their heads to allow optogenetic stimulation of the CEA via optic fibres. These rats underwent 2 days of contextual fear conditioning, after which rats showed freezing responses when exposed to the fear-conditioning box. Exposure of fear-conditioned animals to blue light attenuated their freezing responses. Importantly, when the oxytocin receptor antagonist was injected into the CEA (via the cannulae), blue light failed to attenuate fear responses, indicating that local release of oxytocin in this region mediates these responses.

Finally, using a modified rabies virus expressing enhanced green fluorescent protein, the authors retrogradely traced the cellular origins of the axonal oxytocin-positive terminals in the CEA. Confirming previous results, they found that oxytocin neurons could be traced back to the aforementioned hypothalamic nuclei.

Together, these results reveal how oxytocin reaches the CEA to exert its effects on fear responses. According to the authors, the approaches used in this study may allow investigation into the effects of endogenous oxytocin in other brain regions and on other social behaviours.

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ORIGINAL RESEARCH PAPER Knobloch, H. S. *et al.* Evoked axonal oxytocin release in the central amygdala attentuates fear response. *Neuron* **73**, 553–566 (2012)

FURTHER READING Meyer-Lindenberg, A. *et al.* Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nature Rev. Neurosci.* **12**, 524–538 (2011)