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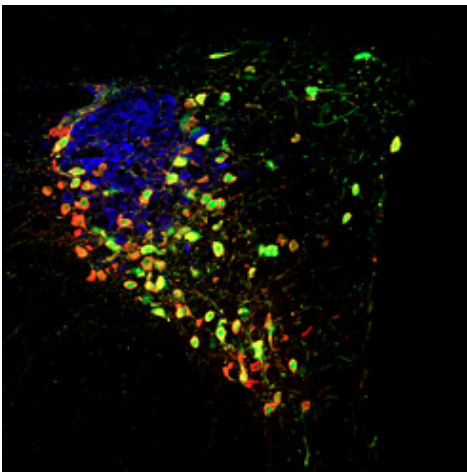
Medicine . Neurosciences

Anti-fear hormone oxytocin transported directly to target sites in the brain

Scientists observe how oxytocin reaches central brain circuits and influences behaviour

February 08, 2012

Cuddle hormone, bonding hormone, anxiety antidote – some of the keywords used to refer to the versatile neuropeptide oxytocin, which has been proven in recent years to exercise a positive influence on central regions of the brain that control our behaviour. However, precisely how this messenger substance from the hypothalamus reaches the areas of the brain that control our feelings and reactions in social situations was completely unclear up to now. Scientists at the Max Planck Institute for Medical Research in Heidelberg and the Swiss Center for Psychiatric Neurosciences in Lausanne have now succeeded in tracing the very long extensions of oxytocin-producing neurons in the rat brain to their target destinations. They also observed how the targeted release of oxytocin in the amygdala region of the brain attenuates the fear response.



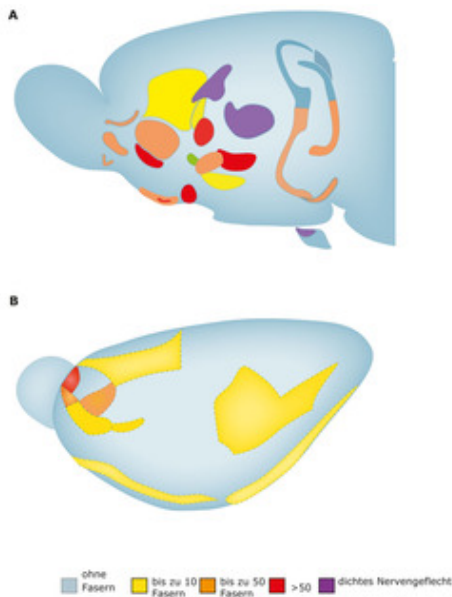
The image depicts cell-type specific fluorescent labeling of hypothalamic oxytocin neurons (green – GFP, red: oxytocin, blue: vasopressin)

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Oxytocin is well researched as a hormone that controls the process of birth and maternal milk flow. It also influences the bond between mother and child and, according to recent studies, our social behaviour in general, for example our trust in other people, loyalty and how we react when we are afraid. The neuropeptide is formed in the neurons of the hypothalamus, the control centre of our vegetative nervous system, and reaches the pituitary gland (hypophysis) via neuronal extensions, where it is stored temporarily and released into the blood when required. The hormone then reaches the target organs, like the womb and mammary glands, via the blood.

But how does the oxytocin reach the central areas of the brain that can control behaviour, for example the amygdala, the part of the brain where fear and stress are controlled? The long-accepted hypothesis that the hormone is released by the dendrites of the neurons in the hypothalamus and reaches the central areas of the brain through diffusion, was not confirmed by the current study. "We were able to see from brain slices that the oxytocin from the neurons in the hypothalamus is transported directly to the target area via ramified and very long axons. From there, it is released locally," explains Peter H. Seeburg, Director of the Molecular Neurobiology Department at the Max Planck Institute for Medical Research. "Moreover, we were able to demonstrate, using behavioural tests, that the hormone released locally in the amygdala actually triggers a fear-attenuating response."

The scientists used a combination of methods in their study: in addition to behavioural tests, they also availed of anatomical, electrophysiological and optical processes. They rendered the oxytocin-producing neurons (OT neurons) and their extensions visible in living animals using the photosensitive protein channelrhodopsin. "What is special about channelrhodopsin is that it activates the neuron when switched on by blue light", says Max Planck Research Group Leader Valery Grinevich in explanation of the ingenious method used. To use this light switch, the researchers specifically introduced the gene for channelrhodopsin and a fluorescent protein into OT neurons. This enabled them to observe these neurons and their extensions under the fluorescence microscope and activate them using blue light.



Distributions of fibers of oxytocin producing neurons from the hypothalamus in other forebrain regions of lactating rats: subcortical (A) and cortical areas (B). The colors depict the density of fibers.

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In the brain slices, the scientists were not only able to demonstrate the path taken by the oxytocin, they were also able to confirm that the locally released oxytocin has an inhibiting influence on the neurons of the amygdala through the neurotransmitter GABA (gamma-aminobutyric acid). The researchers deliberately triggered the release of oxytocin in the amygdala of living animals using blue light, and thereby succeeded in directly attenuating a previously induced state of fear in the rats.

The scientists found the axons of OT neurons from the hypothalamus not only in the amygdala, but also in many other regions of the basal forebrain. This raises the question as to whether the brain has a kind of circuit diagram, based upon which the neurons transmit the versatile hormone to the various target sites. Another question that remains unclear is when the oxytocin opts for the path to the blood via the hypophysis, and when it reaches the regions of the brain that control our behaviour via the neuronal axons and their branches.

Thanks to the new OT-neuron-specific gene constructs, the scientists now have a tool at their disposal with which they can study oxytocin and its effects on behaviour in different regions of the brain in detail for the first time. This could have important consequences for behavioural therapy. Other scientists are already trying to influence behaviour positively using the hormone in the form of nasal sprays. Grinevich remains sceptical about this approach, however: "We still have no proof that oxytocin can reach the brain in this simple way." Thus, a substance that kindles love when dribbled into the eyes or nose, as in Shakespeare's *A Midsummer Night's*

Dream is likely to remain a poetic invention for some time to come.

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