Researchers discover life-long effects of neuropeptides in the brain

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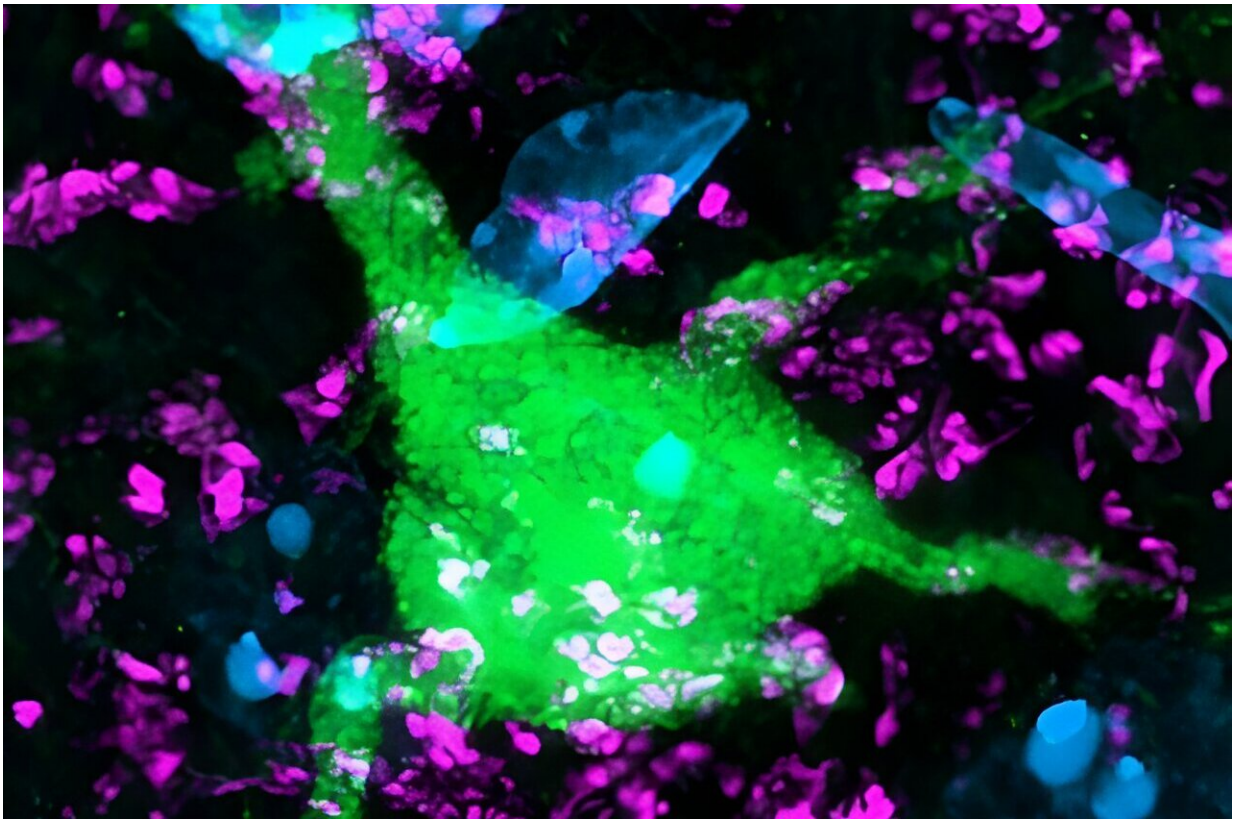

A GFP^+ thalamic neuron (green) apposed by vesicular glutamate transporter 2 $(VGLUT2)^+$ presynapses (magenta) in the infant mouse brain. Nuclei were counterstained with DAPI (light blue). The image was reproduced with modifications from *Nature Communications* (2024). DOI: 10.1038/s41467-024-47054-5. Credit: Zsofia Hevesi, Joanne Bakker

Neuropeptides, which are broadly considered to modulate synaptic communication, can have unique and life-long effects on brain development, particularly the wiring of neuronal circuits.

Researchers at Karolinska Institutet and MedUni Vienna now show that the presence of the neuropeptide galanin during a critical window of brain development is imperative for neurons to connect efficaciously to one another. The study is published in in *Nature Communications*.

Data show that galanin affects sensory development, and is of significance prior to eye opening in rodents. The robustness of the study stems from galanin being effective in a fundamental sensory circuit, the whisker pathway, which in rodents is the primary sensory modality particularly before eye opening.

New family of ligands

The results place an entirely new family of ligands (neuropeptides) onto the map of developmental neuroscience. These ligands are in the nervous system not just secondary to simply modulating the action of powerful fast neurotransmitters (GABA, glutamate, monoamines) but have, in fact, unique actions on their own right. Since neuropeptides act at G protein-coupled receptors, their action is long-lasting and therefore could be particularly sensitive to maternal manipulations through, e.g., breast milk or direct contact (when the mother moves/interacts with her pups).

"The finding that some of the behavioral impairments endure into the adulthood of the offspring in which galanin signaling was impaired highlights the robustness of neuropeptide action," says Tibor Harkany, Professor at the Department of Neuroscience at Karolinska Institutet and MedUni Vienna's Center for Brain Research, who also led the study.

Cellular and in vivo circuit neurobiology studies were performed using

genetic and chemical manipulation of both the expression of the neuropeptide and its receptors. A comprehensive picture of outcomes was built by collecting neuroanatomy, biochemistry, and behavioral neuroscience read-outs.

Short signal-competent proteins

Neuropeptides are a large superfamily of short signal-competent proteins with more than 100 receptors. Some of these receptors produce stimulating and others inhibiting signals.

"Our idea is to test if other neuropeptides could also have developmental impact to build a broader 'principle of action,' and also the contribution of specific receptor systems for signal diversification to distinguish beneficial versus adverse effects," adds Tomas Hökfelt, Professor Emeritus at the Department of Neuroscience, who co-led the study.

Since many peptide receptors were earlier singled out as targets for drug development, drug repurposing could be key in developmental/congenital disorders where galanin and other neuropeptides are involved.

More information: Zsofia Hevesi et al, Transient expression of the neuropeptide galanin modulates peripheral-to-central connectivity in the somatosensory thalamus during whisker development in mice, *Nature Communications* (2024). DOI: 10.1038/s41467-024-47054-5

Provided by Karolinska Institutet