The role of neuropeptides in shaping neuronal activity in hippocampus

Anna Blasiak[1,*], Aleksandra Trenk[1], Kinga Przybylska[1], Anna Gugula[1], Alan Kania[2], Camila de Avila[3], Mohammed Akhter Hossain[4], Anthony J. Intorcia[5], Geidy E. Serrano[5], Thomas G. Beach[5], Diego Mastroeni[3], and Andrew L. Gundlach[4]

[1]*Department of Neurophysiology and Chronobiology, Institute of Zoology and Biomedical Research, Jagiellonian University, Krakow, Poland*
[2]*Department of Neuropeptide Research for Psychiatry, Central Institute of Mental Health, Mannheim, Germany*
[3]*ASU-Banner Neurodegenerative Disease Research Center, Tempe, Arizona, USA*
[4]*The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, Australia*
[5]*Banner Sun Health Research Institute, Sun City, Arizona, USA*
* anna.blasiak@uj.edu.pl

Neuropeptides are highly-diverse signaling molecules that modulate neurotransmission by direct effects on neuronal activity and by modulation of classical transmission. Most neuropeptide-receptor systems affect the activity of neural circuits associated with multiple brain structures, a property linked to their integrative role in the control of complex physiological processes and shaping behavior. Importantly, neuropeptides can also interact with each other at multiple levels, however our understanding of the nature, location, and consequences of neuropeptidergic signaling interactions is still incomplete.

A fascinating, recent discovery is the demonstration of a strong inhibitory influence of the neuropeptide relaxin-3 (RLN3) on magnocellular neurons of the paraventricular hypothalamic nucleus, the main source of oxytocin and vasopressin [1]. RLN3, synthetized in the brainstem, nucleus incertus (NI), is a highly-conserved member of the relaxin-family of peptides and is highly expressed in the brain of rats, mice, non-human primates and humans, along with its cognate receptor RXFP3 [2]. Notably, NI neurons are 'reciprocally' controlled by oxytocin/OTR signaling in rats.

Oxytocin and RLN3 have been shown to regulate a range of common processes, including social interaction, stress responses, food intake, anxiety, and arousal. However, while activation of the oxytocin receptor (OTR), which is G_q-protein-coupled, induces excitatory effects, activation of $G_{\alpha i/o}$-protein-coupled RXFP3, leads to inhibition of neuronal activity. Notably, OTR and RXFP3 share a common effector, M-type K-channels, but their activation exerts opposite effects. Activation of OTR leads to channel closure and cell depolarization, while RXFP3 activation leads to channel opening and cell hyperpolarization.

Co-operation of oxytocin and RLN3 systems is not limited to their mutual 'negative feedback' control. Recent findings indicate that these neuropeptide systems also interact closely within target structures. For example, in the dentate gyrus (DG) of the anterior/ventral hippocampus, an identical population of DG interneurons co-express OTR and RXFP3 mRNA in rat and human brain. Critically, activation of postsynaptic receptors for oxytocin and RLN3 produces opposite excitatory and inhibitory effects, respectively, in the same neurons, indicating an additional level of complexity in the relationship between these neuropeptides. The described mutual dependency between oxytocin and RLN3 networks provide a better understanding of the complex relations between neuropeptide systems, and offer new insights into the neural mechanisms underlying integrated autonomic and complex processes.

Acknowledgements

Funding: National Science Centre, Poland: UMO-2018/30/E/NZ4/00687.

References

[1] Kania A et al. (2020) J Neurosci 40:5362–5375.

[2] Ma S et al. (2017) Br J Pharmacol 174:1034–1048.