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Topic: AS11 Neuroendocrine Systems

THE ENDOLYSOSOMAL CATION CHANNEL TPC REGULATES SOCIAL BEHAVIOR BY CONTROLLING OXYTOCIN SECRETION

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Oxytocin (OT) is a prominent regulator of many aspects of mammalian social behavior and stored in large dense-cored vesicles (LDCVs) in hypothalamic neurons. It is released in response to activity-dependent Ca^{2+} influx, but is mainly dependent on Ca^{2+} release from intracellular stores, which primes LDCVs for exocytosis. Despite its importance, critical aspects of the Ca^{2+} -dependent mechanisms of its secretion remain to be identified. In a recently published paper, using immunostaining, we showed that lysosomes are in close proximity with the OT LDCVs, and that the direct activation of endolysosomal two-pore channels (TPCs) provides the critical Ca^{2+} signals to prime OT release by increasing the releasable LDCV pool without directly stimulating exocytosis. Using radio-immunoassays, we observed a dramatic reduction in plasma OT levels in TPC knockout mice, and impaired secretion of OT from the hypothalamus demonstrating the importance of neuropeptide vesicles priming for activity-dependent release. Furthermore, we showed that activation of type 1 metabotropic glutamate receptors sustains somatodendritic OT release by recruiting TPCs. The priming effect could be mimicked by a direct application of NAADP, the endogenous agonist of TPCs, or a selective TPC2 agonist, TPC2-A1-N. Confocal calcium imaging revealed reduced aspects of Ca^{2+} responses evoked by glutamatergic stimulation in presence of pharmacological inhibitors of TPCs or TPC deletion. Finally, behavioral experiments revealed that mice lacking TPCs exhibit impaired maternal and social behavior, which is restored by direct OT administration. This study demonstrates an unexpected role for lysosomes and TPCs in controlling neuropeptide secretion, and in regulating social behavior. Martucci et al., 2023, PNAS, doi: 10.1073/pnas.2213682120

Declaration of Interest Statement: None

<https://doi.org/10.1016/j.ibneur.2023.08.1568>

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Topic: AS11 Neuroendocrine Systems

SOCIAL STRESS IMPACTS SPEXIN FUNCTIONING BY RECEPTOR, GALR2B, DOWNREGULATION IN THE NILE TILAPIA BRAIN

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Spexin is a relatively new neuropeptide that has been implicated in various neuroendocrine functions including as an appetite-limiting factor and reproductive function inhibitor. Spexin has also been attributed to stress response in the brain, although the information is limited and its downstream targets and effects are still unclear. For example, social stress in the Nile tilapia upregulated the expression of spexin in the brain but it is unknown if its receptors are also affected. Here we studied spexin's receptors, galanin receptor 2a (GALR2a) and GALR2b, in the Nile tilapia. We performed a chronic social defeat paradigm to induce social stress on subordinate males. This employs the natural social hierarchy among male tilapia, which leads to the formation of dominant and subordinate males. A subordinate male was paired with an aggressive, dominant male for five days straight. Brain tissues from the subordinate males were sampled on the fifth day. Using gene expression analysis, we found that *galr2b* receptor was highly expressed in the brain compared to *galr2a*. In socially stressed males, *galr2b* expression was downregulated in the brain, when compared to unstressed control males. No change in *galr2a* was observed under social stress. Social stress-induced regulation of spexin-GALR2b activity may indicate spexin as a neuromodulator of social stress.

Declaration of Interest Statement: None

<https://doi.org/10.1016/j.ibneur.2023.08.1569>

P1564 / #3853

Topic: AS11 Neuroendocrine Systems

DREADD-ING STRESS: USING CHEMOGENETICS TO BYPASS VARIABILITY AND EXAMINE SEX-SPECIFIC VULNERABILITIES TO CHRONIC CRF ACTIVATION

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Chronic lifetime adversity is one of the strongest predictors of neuropsychiatric disease. Further understanding of mechanisms underlying disease risk requires consideration of additional factors that interact with chronic stress, such as biological sex, and is essential for developing novel therapeutic interventions. Current