

Nicotinic activation of NPY/AgRP neurons of the arcuate nucleus and its role in stress and feeding

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In the brain, Neuropeptide Y (NPY) modulates anxiety via amygdalar circuits or regulates energy homeostasis and stress response via hypothalamic nuclei, including the arcuate nucleus (ARC). Within the ARC, the orexogenic NPY/Agouti-related peptide (NPY/AgRP) neurons are responsive to variation of the metabolic state, hormones, GABAergic transmission, and nicotine. Interestingly, nicotine consumption is associated with a reduction of food intake and an increase of the hypothalamo-pituitary-adrenal stress response, whereas NPY release to the hypothalamic paraventricular nucleus (PVN) stimulates feeding behavior. We hypothesize that cholinergic activation of NPY-expressing neurons of the ARC is implicated in the modulation of NPY release. To test this hypothesis, we crossed beta2-flox/flox mice with NPY-IRES-Cre to delete beta2-containing nicotinic acetylcholine receptors (nAChRs) in all the NPY-expressing cells. We used in situ hybridization for NPY and beta2-nAChRs to confirm the presence of nAChRs on NPY/AgRP neurons of the ARC in control animals, and the beta2 deletion in the floxed mutants. Then, we induced stress by restraining and we measured its effect in selected behavioral tasks. Given a dysmorphic association between stress exposure and alterations in feeding, we decided to test male and female mice, both during light and dark regimen. In females, the deletion of beta2-nAChRs increases the susceptibility to daily stressors and impairs the preference for social interaction, while in males it influences metabolism and body weight. The phenotype observed suggests a more complex interplay between the cholinergic system and NPY release, with possible recruitment of other types of nAChRs and compensatory mechanisms that need further investigation.

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