Abstract

Neuronal plasticity is essential for learning, memory, and appropriate adaptations of behavior in response to changes in the environment or the internal state of an organism. Importantly, plastic changes in several neuronal circuits have been implicated to contribute to the regulation of energy balance. One neuronal population that has been identified as an important component of these circuits are hypothalamic agouti-related peptide (AgRP)-expressing neurons. AgRP neurons become active under energy-deprived conditions and their acute activation promotes voracious food consumption. The synaptic input of AgRP neurons is subject to energy state-dependent adaptations resulting in increased activity levels during energy-deprived conditions. Yet, it remains elusive how AgRP neuron output is affected by these neuronal adaptations upon changes in nutrient availability. Moreover, whether AgRP neuron activity and/or the release of particular signaling molecules from their terminals contributes to neuromodulatory effects in their target brain regions is unknown. Therefore, in this thesis a complementary approach that combines optogenetics and electrophysiology was employed to study neuronal plasticity in a key target of AgRP neurons. Specifically, we characterized the properties of gamma aminobutyric acid (GABA)-ergic transmission in the bed nucleus of the stria terminalis (BNST), a brain region that not only integrates hunger-related signals via projections from AgRP neurons, but also receives anxiety-related signals via projections of neurons residing in the central amygdala (CeA). We revealed that fasting as well as the selective activation of AgRP neurons increases functional GABAergic connectivity of AgRP → BNST synapses. In striking contrast, GABAergic transmission of CeA → BNST synapses was profoundly attenuated. Application of gene knock-out and specific re-expression approaches showed that these homo- and heterosynaptic alterations in GABAergic synapses require AgRP neuron-derived neuropeptide Y (NPY). Further *in vivo* studies demonstrated that NPY signaling is in general required for the anxiolytic phenotype of food-deprived mice, yet sufficiency of AgRP neuron-derived NPY in the regulation of anxiety-related behaviors could not be determined. Together, these findings reveal unprecedented aspects of

energy state-dependent changes in neuronal plasticity driven by AgRP neurons in their output regions which might have important implications in the regulation hunger and anxiety signaling, respectively.