ABSTRACT

LOCATION SPECIFIC ADRENERGIC RECEPTOR SIGNALING AND ITS ROLE IN THE REGULATION OF ASTROCYTE GENE EXPRESSION

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The noradrenergic system in the brain has powerful influences on neuronal and glial function that are critical for adaptive changes in brain function that underlie attention, cognition, arousal, and the response to stress. In astrocytes, norepinephrine influences neuroprotective, immunoregulatory, and metabolic processes through activation of G protein-coupled adrenergic receptors which, until recently, were believed to localize exclusively to the plasma membrane. We recently identified functional β1 adrenergic receptors (β1-ARs) localized to the inner nuclear membrane in astrocytes and demonstrated that norepinephrine accesses and activates nuclear β1-ARs via transporter-mediated uptake. This dissertation will test the hypothesis that the nuclear membrane and plasma membrane are distinct signaling platforms with unique contributions to the overall effect of norepinephrine on astrocyte physiology.

In the following studies, I use subcellularly-targeted excitation ratiometric kinase activity biosensors to examine the kinetics and pharmacology of norepinephrine-induced increases in protein kinase A (PKA) and protein kinase C (PKC) activity at the plasma membrane and in the nucleus of primary mouse astrocytes. I demonstrate that within minutes of application, norepinephrine induces rapid increases in PKA and PKC activity both at the plasma membrane and in the nucleus. Further, I provide pharmacological evidence that responses at the two locations are driven by distinct combinations of adrenergic receptor subtypes. Next, I develop a tool using differentially membrane permeable antagonists to attempt to selectively block plasma membrane- and nuclear-localized adrenergic receptor signaling. Lastly, utilizing this pharmacological tool, I test the contributions of signaling at the two compartments to noradrenergic upregulation of protein targeting to glycogen and interleukin-6 mRNA, genes critical in astrocyte glycogen metabolism and inflammatory responses respectively. I present evidence that nuclear-localized β1-adrenergic receptor signaling is required for the effect of norepinephrine on gene expression. These studies demonstrate that norepinephrine initiates distinct signal transduction events at astrocyte nuclei and plasma membranes, and that local receptor-driven signaling events regulate distinct cellular processes related to the supportive functions of astrocytes.