REGULATION AND FUNCTION OF $P2Y_2$ AND $P2X_7$ NUCLEOTIDE RECEPTORS IN THE CENTRAL NERVOUS SYSTEM

Qiongman Kong

Dissertation Supervisor: Dr. Gary A. Weisman

ABSTRACT

It is well known that ATP acts as a classic neurotransmitter in the central nervous system. It is stored in synaptic vesicles, released upon neuronal excitation, and activates both ion channel receptors (P2X) and G protein-coupled receptors (P2Y) on post-synaptic cells. In addition to its role as a neurotransmitter, ATP and other nucleotides are known to be released from injured or ischemic tissue and have been reported to affect inflammatory events in the brain and many other tissues, however, these inflammatory events as well as the subtype(s) of nucleotide receptor(s) influencing these events have not been well defined. This dissertation examines the expression patterns of P2X and P2Y nucleotide receptors in rat primary cultures of cortical neurons (rPCNs), in adult rodent brains, in cerebral ischemia and in collared rabbit carotid arteries. $P2Y_2R$ is up-regulated in response to cytokine stimulation in rPCNs *in vitro* and after collar transplantation around rabbit carotid arteries *in vivo*. Moreover, *in vivo* studies in the collared carotid artery model indicate the involvement of $P2Y_2Rs$ in the development of intimal hyperplasia. Based on these studies, particular emphasis was placed on delineating the role of the $P2Y_2$ receptor subtype in neuronal inflammation and the $P2X_7$ receptor subtype in neuronal apoptosis in the central nervous system. In the rat primary cultures of cortical neurons, activation of the $P2Y_2R$ and $P2X_7R$ caused α-secretase-dependent APP processing and caspase8/9/3-dependent apoptosis, respectively. These results suggest the important roles of P2 nucleotide receptors ($P2Y_2R$ and $P2X_7R$) and their associated signaling pathways in regulating neuronal inflammation and apoptosis in brain disorders and neurodegeneration.