James & Esther King Biomedical Research Program

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Project Title: Regulation of GABA Biosynthesis in the Brain

Project Summary: The communication between neurons is mediated through neurotransmitters (NT). There are two types of NT dependent on their effect on the neurons. The excitatory NT stimulates neurons, whereas the inhibitory NT suppresses neurons. For the brain to function properly, it needs to maintain a precise balance between excitation and inhibition. The most abundant excitatory and inhibitory NT are glutamate and gamma-aminobutyric acid (GABA), respectively. Excessive stimulation by glutamate is believed to be the underlying mechanism for many neurological diseases including stroke-induced brain injury. This grant is designed to understand how the brain maintains its proper function through the study of GABA synthesis in the brain. GABA is synthesized from glutamate by an enzyme called glutamate decarboxylase (GAD). GAD converts glutamate to GABA, and hence plays a crucial role in determining the overall state of excitation in the brain. How GAD is regulated under physiological and pathological conditions remains elusive. However, we know that protein phosphorylation is a common mechanism that regulates the function of many proteins, and previous studies in our laboratory have shown that protein phosphorylation plays an important role in the regulation of GAD activity in the brain. Therefore, this study is designed to further investigate the phosphorylation of GAD under normal and pathological conditions such as stroke. Specifically, we will identify the phosphorylation sites in GAD and elucidate the function of GAD phosphorylation under physiological and stroke conditions. Studies show that cigarette smoking is an important risk factor for stroke. Many lines of evidence clearly demonstrate that cigarette smoke damages the cerebrovascular system and greatly increases the risk of stroke. Stroke is a leading cause of death and long-term disability. There is overwhelming evidence linking excessive glutamate excitation to the development of brain damage following stroke. However, no clinically effective therapeutic intervention has been developed yet. Many drugs that are designed to block glutamate function known as glutamate antagonist have been developed and failed in clinical trials. While many neurotransmitter systems may play a role in stroke-induced brain damage, the GABA system may be of particular importance because of its inhibitory function in opposition to the excitatory function of glutamate. Compared to glutamate, GABA has received relatively little attention in the area of therapeutic intervention for stroke-induced brain damage. However, many of the drugs that enhance GABA function have been shown to have beneficial effects in animal models of stroke. These drugs have already been used clinically for other conditions, e.g., anxiety and seizures, with few side effects. Thus, drugs that can increase GABA function may be attractive candidates for further development as potential therapeutic agents for stroke. Information gained from this grant will enable us to develop a therapeutic strategy to maintain the proper level of brain excitation and prevent brain injury due to excessive excitation by glutamate as in the condition of stroke. Since cigarette smoke increases the risk of stroke, and stroke-induced brain injury can be minimized by enhancing GABA transmission, the regulation of GABA biosynthesis in the brain is therefore relevant to cigarette smoke.

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