CHAPTER I

INTRODUCTION

1. Background and Rationale

Diabetes mellitus is one of the most prevalent chronic diseases affecting millions of people around the world (World Health Organization, 1998). Several complications of diabetes mellitus can cause disability. For instance, retinopathy can result in blindness, nephropathy can progress to chronic renal failure and renders patients dependent on dialysis. Hence, treatments of diabetes and its associated complications will account for substantial medical expenditure on health care.

Neuropathy is another major complications of diabetes characterized by peripheral nerve dysfunction in several aspects. The most common manifestation of diabetic neuropathy is abnormal sensory functions in the distal parts of the extremities (distal symmetrical sensory polyneuropathy), especially toes and feet prior to fingers and hands (The Diabetes Control and Complications Trial Research Group, 1995). Reduced pain perception particularly in the feet can lead to repeated trauma and ulceration which is aggravated by the impairment of vascular supply and immune functions required for normal wound healing. Severe foot ulcer can result in amputation and renders patients disabled.

Although neuropathy has been studied by many investigators, the molecular mechanisms underlying this abnormality are still unclear. MAPKs (mitogen-activated protein kinases) are a family of protein kinases comprised of extracellular signal-regulated kinase(ERK),c-Jun NH_2-terminal kinase (JNK) and p38 kinase. These three subfamilies of MAPKs lie in the protein kinase cascades responding to extracellular stimuli ranging from growth factors and various kinds of stress. MAPKs have been shown to implicate in cell proliferation, differentiation and cell death depending on cell types and stimuli (Pearson et al., 2001). The cross-talk and divergence of the cascades allow for the co-ordination between MAPK and other signaling pathways resulting in a variety of cellular responses.

Accumulating evidence suggests the participation of MAPKs in the diabetic neuropathy. Treatment of diabetic rats with p38 inhibitor (SB 239063) can prevent neuronal dysfunction (Agthong and Tomlinson, 2002; Price et al., 2004). ERK was activated in primary sensory neurons cultured in high glucose condition and its inhibition resulted in decreased neuronal death (Purves et al., 2001). According to the above evidence,it is possible that ERK plays a deleterious role in diabetic neuropathy. However, inhibition of ERK and its effect on diabetic neuropathy has not been studied. Therefore, the main objectives of this study were

1. To study the effects of ERK inhibition on reduction of nerve conduction velocity observed in diabetic rats.

2. To study the effects of ERK inhibition on structural abnormalities in the peripheral nevous system (PNS) of diabetic rats.

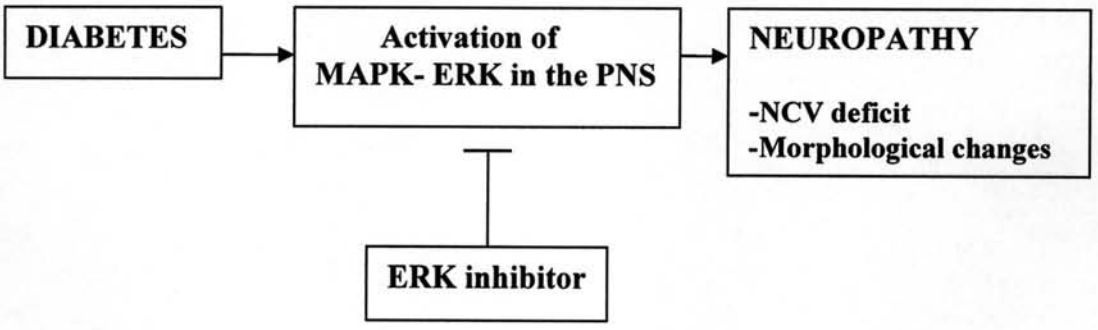
2. Research Question

Does inhibition of ERK affect diabetic neuropathy in rats?

3. Hypothesis

The inhibition of ERK attenuates functional and structural abnormalities in the PNS of diabetic rats.

4. Conceptual Framework



5. Key Words

Diabetic neuropathy, ERK, u0126

6. Expected Benefits and Applications

If the inhibition of ERK in the PNS shows beneficial effects, the ERK inhibitor might be the potential drug for treating this complication of diabetes. The data will also form the basis for future clinical trial.