CHAPTER I
INTRODUCTION

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Diabetes is the most common metabolic disorder, including hyperglycemia and hyperlipidemia. Moreover, diabetes precipitate the onset of both micro- and macrovascular diseases. Diabetic microangiopathy is presented the morphological and functional alterations of microvessels (Tooke JE,1989; Cester N et al.,1996). Interestingly we have found that diabetes produces thickening of the capillary basement membrane in rats (Jariyapongskul A et al.,1997) and Cester N et al(1996) have also found the weakening of intercellular junction and endothelial cell degeneration in diabeteic animals. Functionally,diabetes produces an increase in endothelial permeability (Stauber WT et al., 1981). In addition, we have demonstrated the impairement of cerebral autoregulation response to hemorrhagic hypotension in streptozotocin(STZ)-induced diabetic rats (Jariyapongskul A et al.,1996). Clinically, diabetic microangiopathy leads to retinopathy and glomerular dysfunction and possible contributes to cerebrovascular dysfunction, including stroke. It is known that diabetic patients are at an increased risk of hypertension and stroke (Bell DSH, 1994). More than one fifth of stroke deaths in the population can be attributed to diabetes, more in women than in men (Tuomilehto J et al., 1996). Direct and indirect evidence shows that diabetic patients with neuropathy have reduced neural blood flow and endoneurial hypoxia (Tesfaye S et al., 1994; Newrick PG et al., 1986). Although, the mechanisms responsible for the vascular dysfunction, including reduced organ blood flow remain unclear. However,

it has been hypothesized that endothelial dysfunction is one major possible mechanism for microvascular dysfunction. The vascular endothelium has a key role in maintaining homeostasis of the vasculature through the synthesis of vasoactive substances, including nitric oxide that modulate vascular tone, inhibit platelet aggregation and vascular smooth muscle cell proliferation (Moncada S et al., 1991, Gary UC et al., 1989).

The consistent finding of various studies which are carried out in conduit arteries of diabetic animals is the presence of endothelial dysfunction. Especially, the most common is characterized by the impairment of endothelium-mediated vasodilation in response to acetylcholine. Diabetes-induced endothelial dysfunction serve as a major initiating process leading to the development of diabetic vascular disease involving both large and resistance arteries. Hyperglycemia which is a common feature of diabetes, has been reported to be one of the importance causes of vascular endothelial dysfunction. As the previous investigations have demonstrated that hyperglycemia play a crucial role to impair endothelium-dependent vasodilation (Cohen RA, 1993; Tesfamariam B, 1990; Ruderman NB, 1992).

Although the mechanisms that mediate endothelial dysfunction during diabetes are not completely defined, it is likely that hyperglycemia the hallmark of diabetes mellitus, may initiate the vascular endothelial dysfunction. Among the sequelae of hyperglycemia, excess oxidative stress has captured considerable attention as a potential mechanism for this dysfunction in diabetes (Diederich D et al., 1994; Guigkiano D et al., 1996).

Increased production of oxygen-derived free radicals and decreased antioxidant defense mechanisms have been described in diabetes (Tuomilehto et al., 1996). There are many metabolic pathways which could increase the generation of free radicals from hyperglycemia.

Elevations in glucose concentration may enhanced production of oxygen-derived free radicals via cyclooxygenase pathway (PGH_2) by oxidation of intermediate products (Bucala R et al., 1991), indirectly by oxidation of advanced glycosylation end products (AGE_s) (Gryglewski et al., 1986) and alteration of polyol pathway activity also lead to the increase of oxygen free radicals.

Up to now, the antioxidants have become a center of interest for their role on prevention of diabetic vascular diseases. Several studies in both diabetic patients and experimental induced diabetes have shown these preventive effects of many antioxidants, including vitamin C. Vitamin C (ascorbic acid) is one of the most powerful natural antioxidant in human. With its antioxidant property, vitamin C can scavenge oxygen-derived free radicals and spares other endogenous antioxidants from consumption (Block G et al., 1991; Retsky KL et al., 1989). It has been reported that plasma and tissue levels of vitamin C are 40-50% lower in diabetic compared with nondiabetic subjects (Yue DK et al., 1989). Mechanism by which vitamin C improve endothelial dysfunction is not clear. However, several studies demonstrated that the improvement in endothelium-dependent vasodilation in diabetic subjects is probably mediated by the ability of vitamin C to scavenge excess superoxide anions and, there by, decrease nitric oxide inactivation (Nishikimi N, 1975; Som S et al., 1983).

From the point of views it can be concluded that both morphological and functional vascular abnormalities have been demonstrated in human and animal models of diabetes mellitus. The increased oxygen-derived free radical mediated by hyperglycemia is an important factor for vascular endothelial dysfunction. At present there is no report about the study of antioxidant effects of vitamin C directly on cerebral endothelial dysfunction in diabetes mellitus. Only a few of the previous studies have suggested that the more prolongation of diabetic state, the more increase incidence of cerebrovascular abnormalities including stroke. Moreover, several investigators suggested that endothelial cells of cerebral blood vessels are functionally and morphologically altered during diabetes(Johnson PC et al., 1982; Mayhan WC, 1989). Therefore, the present study major objective to verify the effects of the antioxidant, vitamin C, especially, on these abnormalities of both endothelial functions and vascular structural changes in cerebral microcirculation by using the intravital microscopic and electron microscopic technique, respectively. In addition, the possible mechanism(s) for these findings will be proposed.