CHAPTER II

RATIONALE

Isolated beating heart model

The isolated beating heart preparation was developed by Langendorff many years ago. The physiological properties of this model have been studied in detail by many investigators. The model has been used for many different types of studies, including pharmacologic, biochemical and cardiomechanics studies.

Because of the wide acceptance and use of this model, the isolated beating heart was chosen as a physiological model in this study. Especially, the isolated beating heart allows directassess of left ventricular contraction without interference of central neural and hormonal effects.In STZ-treated rats the factors, such as lesions of central neural autonomic responses might interfere with the contraction measurement. Therefore, the interpretation of the results becomes very complex, if the study is done in an intact heart model due to many additional factors which may become important.

Streptozotocin (STZ)-treated rat model

The experimental model of diabetes mellitus which was used in this study was induced by a single intraperitoneal dose of streptozotocin (STZ) (65 mg/kg body weight). The STZ-treated rat model is considered to be an experimental model that closes resembalance to insulin-dependent diabetes mellitus in humans. With a single

injection of STZ,the rats become hyperglycemic and hypoinsulinemic within 24-48 hours, which was also observed in this investigation. The diabetogenic action of STZ was by induceing B-Cell damage through the biochemical events caused DNA strand breaks. Such that leadto a critical depletion of nicotinamide dinucleotide (NAD) through the complex mechanism involving more than one type of enzyme (Wilson et al., 1984).

Cilazapril (Angiotensin-converting enzyme inhibitor agent)

The chronic cardiovascular complications of diabetes mellitus included hypertension, atherosclerosis, myocardial dysfunction. The renin angiotensin system, especially AngII, may potentially play a key role in these pathologic processes, and thus, contribute to the development of diabetic cardiovascular complications. Some of reported about their actions on ACE-inhibitors and some direct renin-inhibitors were preventing slowing the progression of these complications, especially, the reduction of left ventricular hypertrophy and of vascular proliferation (Willa, 1992).

The angiotensin-converting enzyme (ACE) splits off two amino acids from the biologically in active Ang I to from the octapeptide Ang II, which is a potent vasoconstrictor. The ACE was found primarily on the pulmonary endothelial cell surface. In present, ACE was also identified in most peripheral tissues such as vessel walls, kidneys, adrenals, heart, and brain as showed in Figure 2.1 (McAreavey and Robertson, 1990).

The renin-angiotensin system plays a central role in the regulation of blood pressure as showed in Figure 2.2. In this system, Ang II is known as a key compound. Ang II could elevate systemic blood pressure through its three actions; 1) on stimulating sympathetic system, 2) on inducing direct vasoconstriction, and 3) on increasing secretion of aldosterone which caused more salt and water retension (Kenneth and Joseph, 1990). Besides this vasoconstriction effect, Ang II has been recently defined as a trophic factor which could develop hypertrophy of hearts and blood vessels. Myocardial Ang II-receptors was identifined in isolated cardiac myocytes and was showed a high affinity with Ang II (Baker et al., 1984) In 1983, Khairallah and Kanabus reported that Ang II might help in regulating myocardial protein synthesis. Until 1991, Katz and his co-workers had confirmed this role of Ang II and named cardiac renin-angiotensin system as a growth regulator. Interestingly, however, the dose of ACE-inhibitor in use of reducing blood pressure was indeed higher than the dose of ACE-inhibitor used to prevent left ventricular hypertrophy (Lindpaintner and Ganten, 1991).

Cilazapril which is a kind of ACE-inhibitor agents was chosen to use in this investigation. Cilazapril is a hydrophilic compound and its active form is cilazaprilat as showed in Figure 2.3 (Kleinbloesem et al., 1989).

In 1989, Clozel and his co-workers showed the ability of cilazapril in reducing vascular hypertrophy in spontaneously hypertensive rat model. This effect of cilazapril was later confirmed by Powell et al. (1989) and

Clozel et al. (1989). It was indicated that the effect of cilazapril on the reduction of vascular hypertrophy was actually the action of cilazapril directly on the vascular smooth muscle. Besides these studies using hypertensive rat models, in the model of balloon catheter-induced vascular injury of the rat carotid artery (Wolfgang et al.,1991) also indicated that the neointima proliferation process could be inhibited by the administration of cilazapril.

According to these suitable roles of cilazapril, it was chosen to use as a ACE-inhibitor in this investigation. Especially, the effects of cilazapril associated with diabetic cardiovascular complications has not yet been demonstrated by any other investigations. The dose of 10 mg /kg body weight of daily oral feeding of cilazapril was used in this investigation. This dose was the same as Sebastien et al., (1991) had used in his study on "Cilazapril inhibits wall thickening of vein bypass graft in the rat".

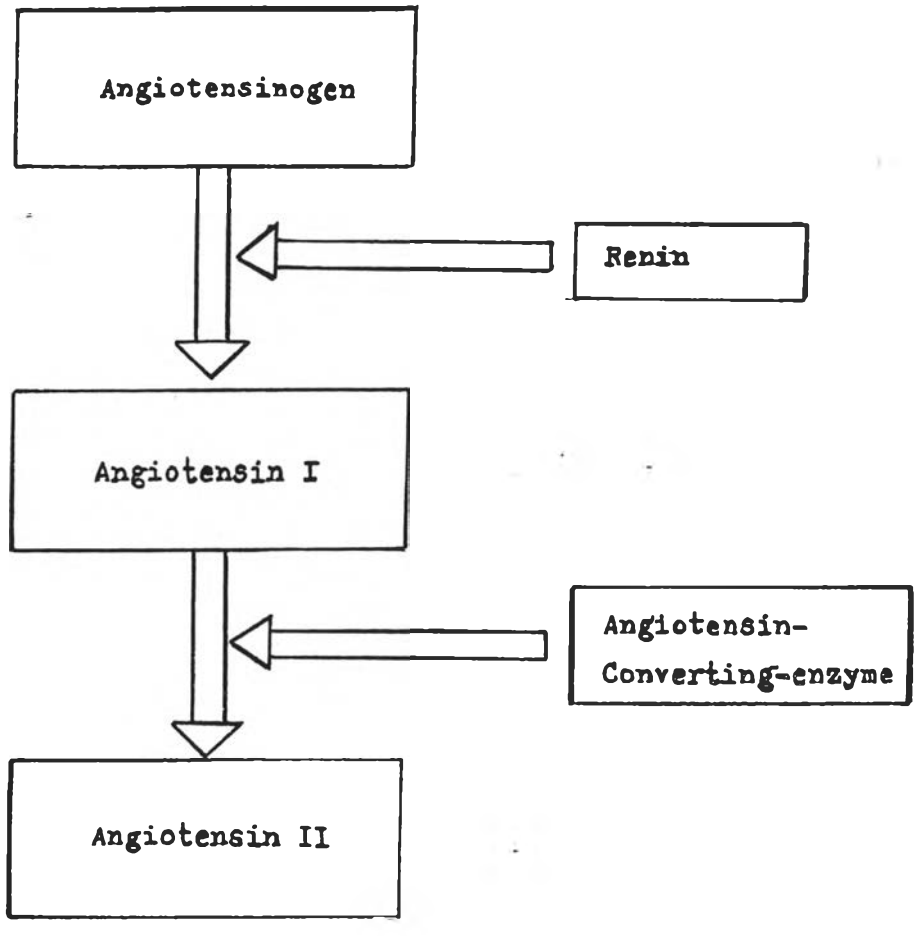

Figure 2.1 Diagram of Renin-angiotensin system
(From McAreavey and Robertson, 1990).

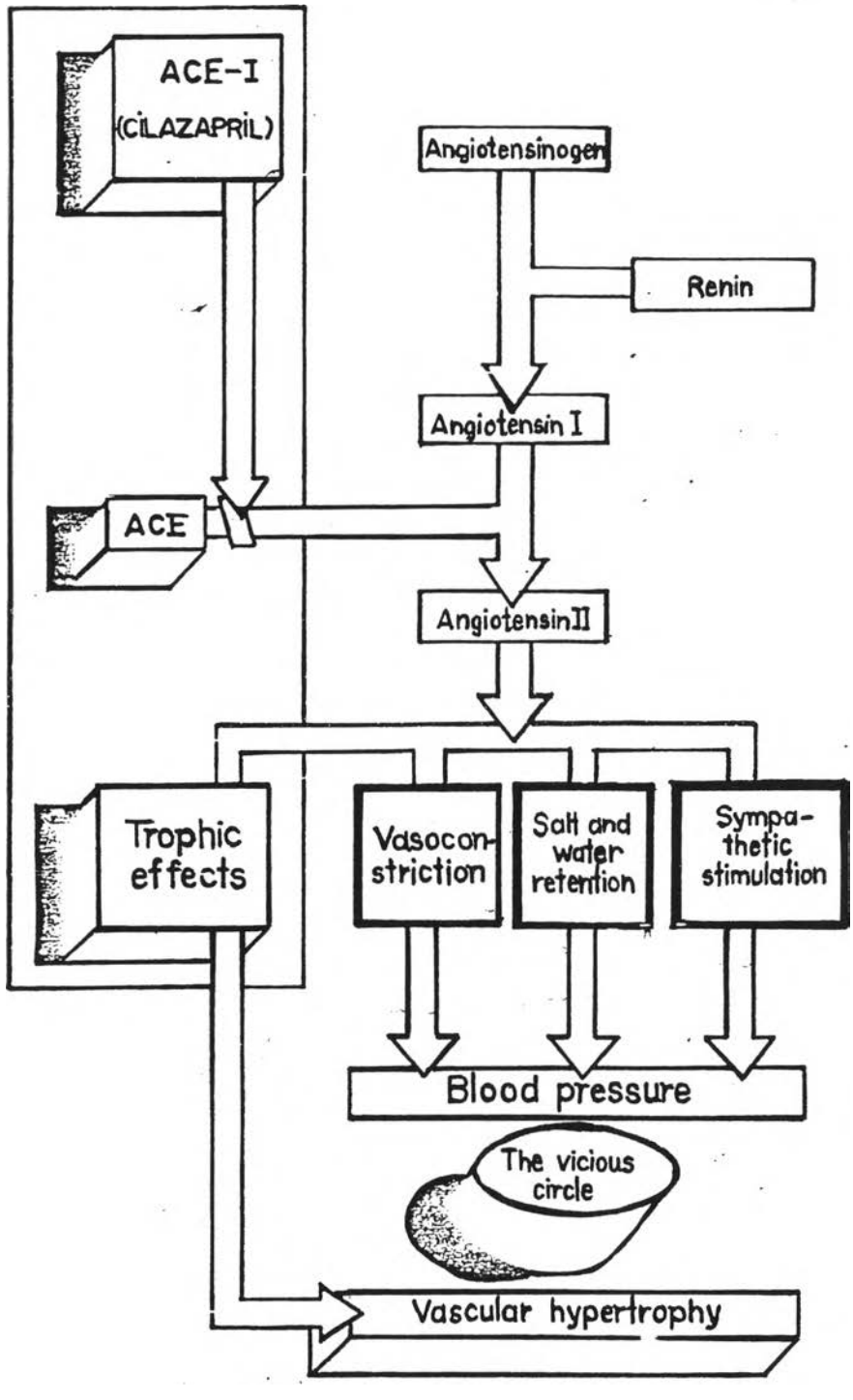

Figure 2.2 The renin-angiotensin-aldosterone system and the mechanism of action (From Kenneth and Joseph, 1990).

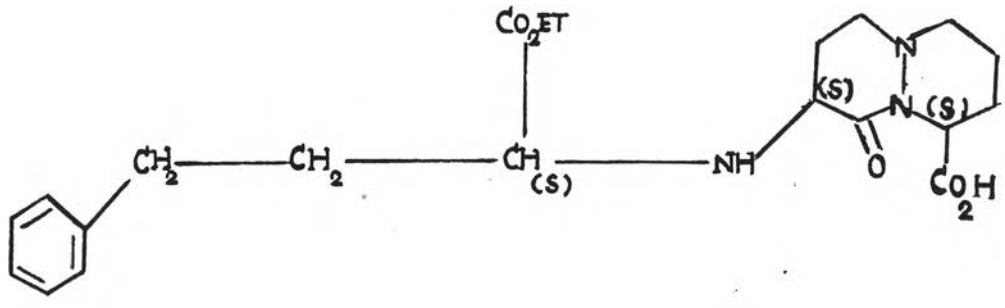

Figure 2.3 Structural formula of cilazaprilat, the active metabolite of cilazapril (From Kleinbloesem et al., 1989).