CHAPTER II

RATIONALE

Isolated beating heart model

The isolate beating heart preparation was developed by Langendorff many years ago (McDonagh PE et al., 1984). The physiological properties of this model have been studied in detail by many investigators. The model has been used for many different type of studies, including phamacologic, 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 direct assess 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 mearsurement. 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 imporance.

Streptozotocin (STZ)-treated rat model

The experimental model of diabetes mellitus which was used in this study was induced by a single intraperitoneal (i.p.) dose of streptozotocin (STZ) (65 mg/ kg. BW). The STZ- treated rat model is considered to be an experimental model that closes resemblance to insulin dependent diabetes mellitus in humans. The diabetogenic action of STZ was detected in Upjohn Lab-Oratories. The mechanism of STZ diabetogenicity has been accumulated. Its nitrosourea moist facilitated its

transport across the cell membrane, inducing β-cell damage through the biochemical events caused DNA strand breaks. Such that lead to a critical depletion of nicotinamide dinucleotide (NAD) through the complex mechanisms involving more than one type of enzyme (LeDoux SP et al., 1988). Because of the glucose moiety of the STZ-molecule, its toxicity is sequestered in beta-cells in preference to other cells and, there, STZ causes beta-cells specific damage. Especially, damage to myocardial cells associated with or cause by STZ has not been demonstrated by any investigation.

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 reports about the actions of ACE-I and 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 renin angiotensin system plays a central role in the regulation of blood pressure as showed in Fig. 2.1. 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 . Angiotensin II has been shown to promote growth of vascular smooth muscle cell. AngII is converted from AngI by angiotensin converting enzyme (ACE) as showed in Fig. 2.2. ACE is a protease with a zinc group, hence being a metalloprotease (Ehlers and Riordan, 1989). There is a single zinc atom at

the high affinity binding site, the site that interacts with AngI or the ACE-I. ACE was also identified in most peripheral tissue such as vessel walls, kidneys, adrenals, heart and brain (McAreavey and Robertson, 1990).

Cilazapril which is one of ACE- I agents was chosen to use in this investigation. Cilazapril is a product, being converted to its active form cilazaprilat as showed in fig. (2.3),(Kleinblosem et al., 1989), which has a long terminal half life with a long duration of action (Natoff et al. 1985; Deget and brogden, 1991).

Inhibitory effects of cilazapril on the renin angiotensin aldosterone system have been studied in various animal models including rats, dogs, and baboons. Potent ACE-I was observed in all models following oral and intravenous administration of cilazapril. As a consequence of ACE-I, plasma concentrations of AngII and III are decreased while those of AngI are increased. Subsequently, as a result of loss of feedback inhibition by AngII, plasma renin concentrations are increased (Nakamura et al. 1988).

The effects of cilazapril on the renin-angiotensin-aldoseterone system have been determined in healthy volunteers and in patients with hypertension. Acute effects of orally administered cilazapril included decreases in plasma concentrations of AngII and aldosterone, and increase in plasma concentration of angiotensinI and plasma renin activity (Burnier et al. 1989; Nakashima and kanamura 1988).

The blood pressure lowering effects of cilazapril have been studied in patients with hypertension. In spontaneously hypertensive rats(SHR) treated with cilazapril, single oral dose of 0.3 and 3 mg/kg reduced aortic blood pressure by 10% and 28%, respectively (Nakamura et al. 1988). Cilazapril has been shown to improve left ventricular diastolic function in patients with left ventricular hypertrophy (Marmur et al. 1989) and during long term treatment of hypertension (Sanchez et al. 1989).

Using a recently introduced technique of radio chemical myocardial imaging, myocardial activity differences between excercise and resting images in patients with stable angina of effort were higher after a single dose of cilazapril than after placebo. These findings were considered indicative of increased segmental myocardial perfusion (Gasic et al. 1990).

Cilazapril has produced sustained beneficial haemodynamic effects in patients with congestive heart failure (kiowski et al. 1990). Hypertrophy of the tunica media (Folkow., 1982). Lower of arterial pressure does not necessary reverse these vascular changes (Clozel et al. 1990), although they can be influenced by some antihypertensive drugs. The effect of 4 months treatment with cilazapril 10 mg/kg/day (a dosage higher than that required for ACE inhibition on medial hypertrophy) was studied in spontaneously hypertensive rats (SHR), and cilazapril was found to decrease the arterial wall thickness: diameter ratio relative to placebo in coronary arteries (Clozel et al. 1989 a,b). In a normotensive rat model, cilazapril reduced intimal proliferation (neointima formation) following carotid artery wall injury. Cilazapril 10 mg/kg daily administered 6 day before and 14 days after balloon injury demonstrated a marked preventive effect on myointimal proliferation.

The decrease in arterial pressure elicited by cilazapril did not appear to be the main factor contributing to prevention of neointima formation, since verapamil,despite decreasing arterial pressure,did not prevent neointima formation (Powell et al., 1989). It has been suggested that cilazapril may inhibit local formation of angiotensinII that stimulates smooth muscle cell growth and that ACE inhibition may modulate growth factor interactions with angiotensinII. Wolfgang Linz, in 1992 has been demonstrated that rats with aortic constriction treated with a non-antihypertensive dose of ramipril (10 μ gm/kg/day) showed the same prevention and regression of cardiac hypertrophy as groups receiving the antihypertensive dose (1mg/kg/day). This may indicate local cardiac effects of the renin-angiotensin system.

According to these suitable roles of cilazapril, it was chosen to use as a ACE-inhibitor in this investigation. The effect of cilazapril was later confirmed by Ampom Jariyapongskul (1994). it was indicated that hypertension, myocardial hypertrophy and coronary arterial wall thickening of STZ-rats could protected by cilazapril 10mg/kg. BW., orally for 16 weeks at 1 day after diabetes was induced. However, diabetic patients who have been cured in hospital usually found that they have long time of diabetic stage until have cardiovascular disease at this time. Ampom., 1994 indicated that at 8 weeks after diabetes was induced, cardiovascular morphologic changes were significantly different than the age matched controls.

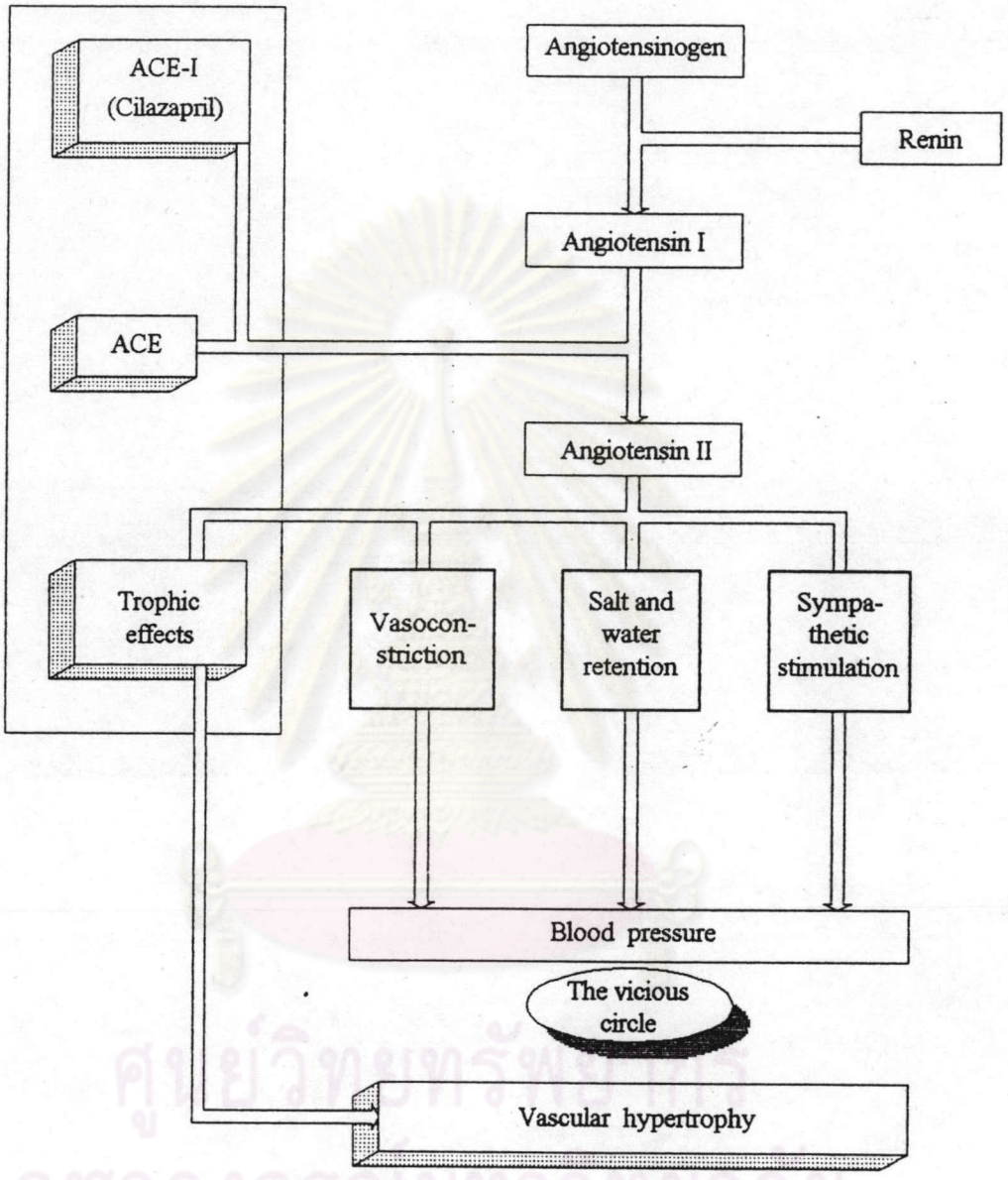

Figure 2.1 The renin-angiotensin-aldosterone system and the mechanism of action (From Kenneth and Joseph, 1990).

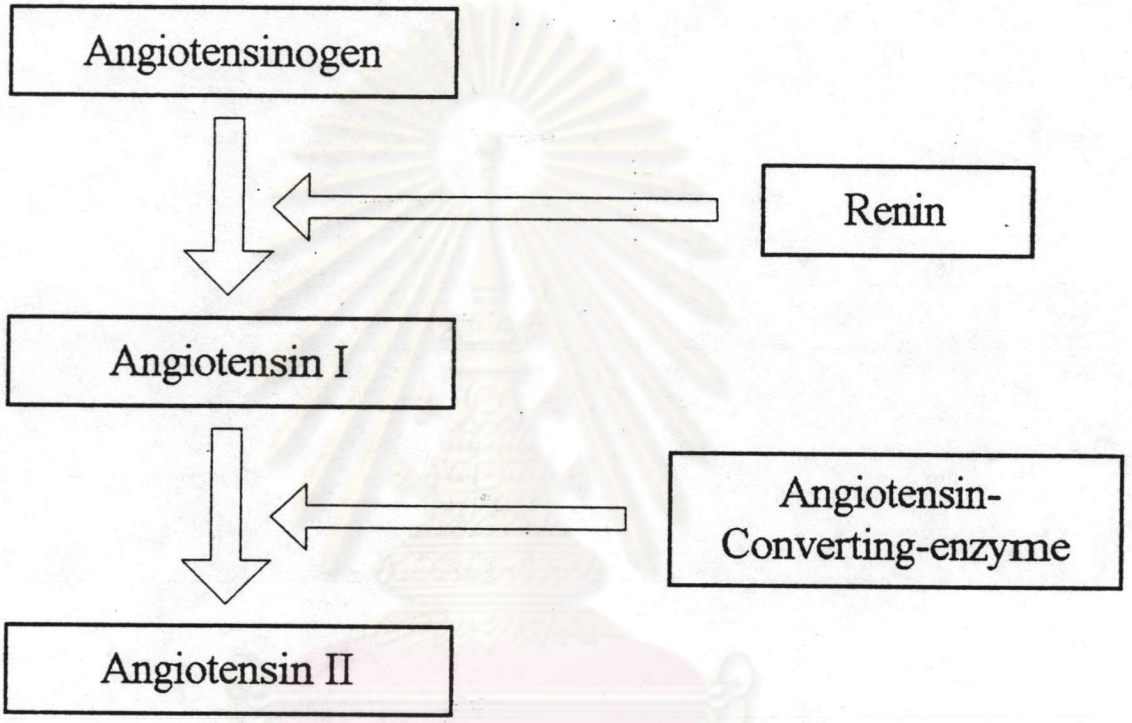

Figure 2.2 Diagram of Renin-angiotensin system (From McAreavey and Robertson, 1990).

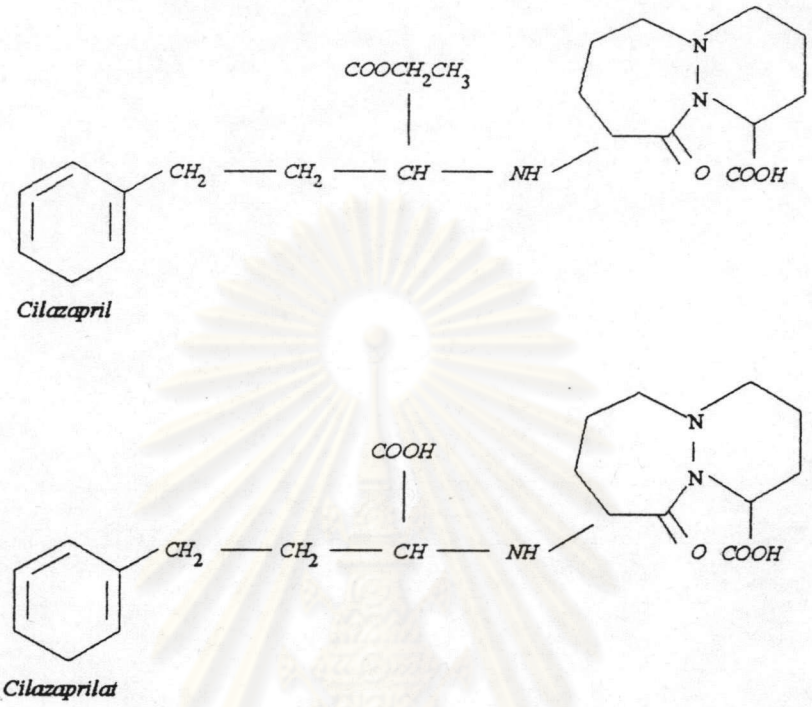

Figure 2.3 Structural formula of cilazaprilat, the active metabolite of cilazapril (From Kleinbloesem et al., 1989).