

CHAPTER II

Rational

Streptozotocin (STZ) - treated rat model

Streptozotocin is a broad - spectrum antibiotic, is isolated from Streptomyces achromogenes . It destroys the β - cells after single injection (Rerup, C.C. 1970.). The molecular structures of STZ is shown in Figure 2.1 . Streptozotocin induces diabetes in rat, dog and other animals. Diabetogenic dose are different species. In the rat, using a single intravenous dose is range from 45 - 55 mg. per kg but in male Wistar Furth rat, using intravenous dose of 55 mg. per kg dissolved in saline at concentration of 1 ml. per kg. can produced diabetes (Hebden, et al. 1990.). The mechanisms of streptozotocin lead to reduce of the cellular-NAD content in several tissues and the effect is particularly harmful to the β - cells. The end result cellular necrosis is the end result. The NAD depletion is link to stimulation of the activity of the nuclear enzyme poly (ADP - ribose) synthase , which is involved in the excision and repairing of broken DNA stands. These mechanisms are required NAD as substrate (Riflin and Porte . 1991.).

Calcium channel blocker (Calcium antagonist)

Calcium channel blocker may be classified into four different groups according to their underlying chemical structures : phenylalkylamines, diphenylalkylamines and dihydropyridines (nifedipine, nimodipine, nicardipine). In the present study, dihydropyridine (nicardipine) is selected as the treatments. The basic mechanisms of action of these classes lie in their abilities to prevent the movement of calcium ion from the extracellular to the intracellular space. Calcium plays a fundamental role in the excitation of the heart and also in the contraction of smooth muscle cells (Ling, T. 1984.).

The physiological role of calcium in the excitation - contraction process explains the cardiovascular effects of calcium channel blockers. These effects include the decrease of inotropic chronotropic in cardiac tissue and vascular smooth muscle relaxation (Eugene, 1987.). The molecular structure of nicardipine is showed in Figure 2.2 and the effects of nicardipine on the cardiovascular system is shown in Figure 2.3. In 1984, Ohata and his co-workers demonstrated that 10 mg/kg/BW of nicardipine could decrease a total serum cholesterol and LDL but it was increase HDL (high density lipoprotein) cholesterol in normal rats. Since LDL is one of a risk factors of atherosclerosis, nicardipine which reduced the LDL level may be anti-atherogenic.

Role of Renin - angiotensin system.

Renin is an enzyme, it acts enzymatically on another plasma protein, a globulin called renin substrate (angiotensinogen) to release a 10 - aminoacid peptide, angiotensin-I. An angiotensin-I has mild vasoconstrictor property. However, its property is not significantly enough to cause functional change in circulatory function. After the formation of angiotensin - I which originated from angiotensinogen by using renin, angiotensin - I will be converted to angiotensin II by angiotensin converting enzyme (ACE) (Guyton, 1996). ACE is found in the vascular endothelium of the lungs, also in the endothelium of other vascular beds and in many other tissues including the myocardium and the coronary arteries. The converting enzyme is nonspecific because it not only converts angiotensin-I to angiotensin-II but inactivates bradykinin, hence the alternate name of kininase. The diagram of Renin-angiotensin system is showed in Figure 2.4.

In the previous study done by our laboratory (Udayachalerm, 1995), the prevention of diabetic cardiovascular complications using daily oral feeding of cilazapril (10 mg/kg/BW) has been demonstrated in 16-weeks STZ-rats. It has been hypothesized from their study that cilazapril could retard these diabetic cardiovascular complications according to their actions as an inhibitor of vascular growth promoting factor and also on its effect on bradykinin synthesis. The molecular structure of cilazapril is showed in Figure 2.5.

Therefore, in this present investigation, we would like to make a further study on the synergistic effects of combining cilazapril and nicardipine especially on the prevention of diabetic cardiovascular complications. Since the combination of these two agents might have the beneficial effects as mention earlier.



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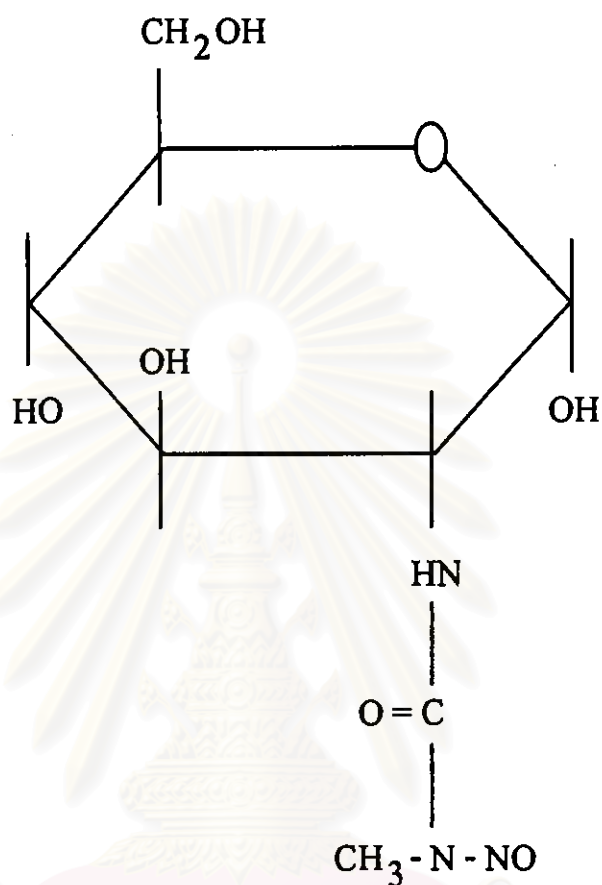


Figure 2.1 The molecular structure of streptozotocin (Rifkin, 1990).

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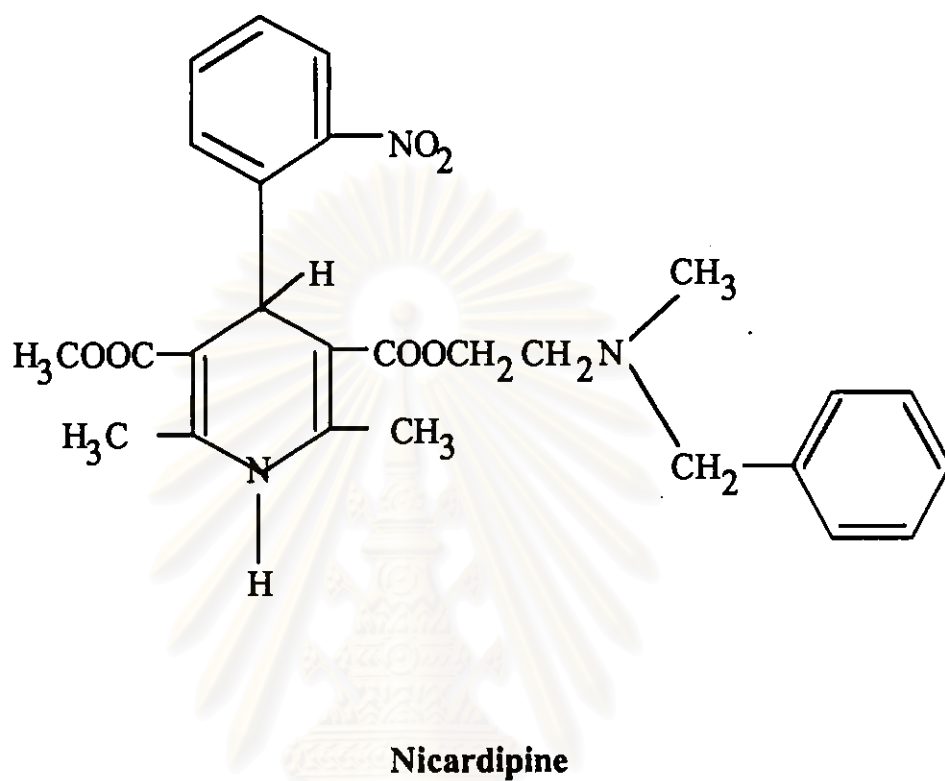


Figure 2.2 Chemical structure of nicardipine (Eugene, M. 1987.)

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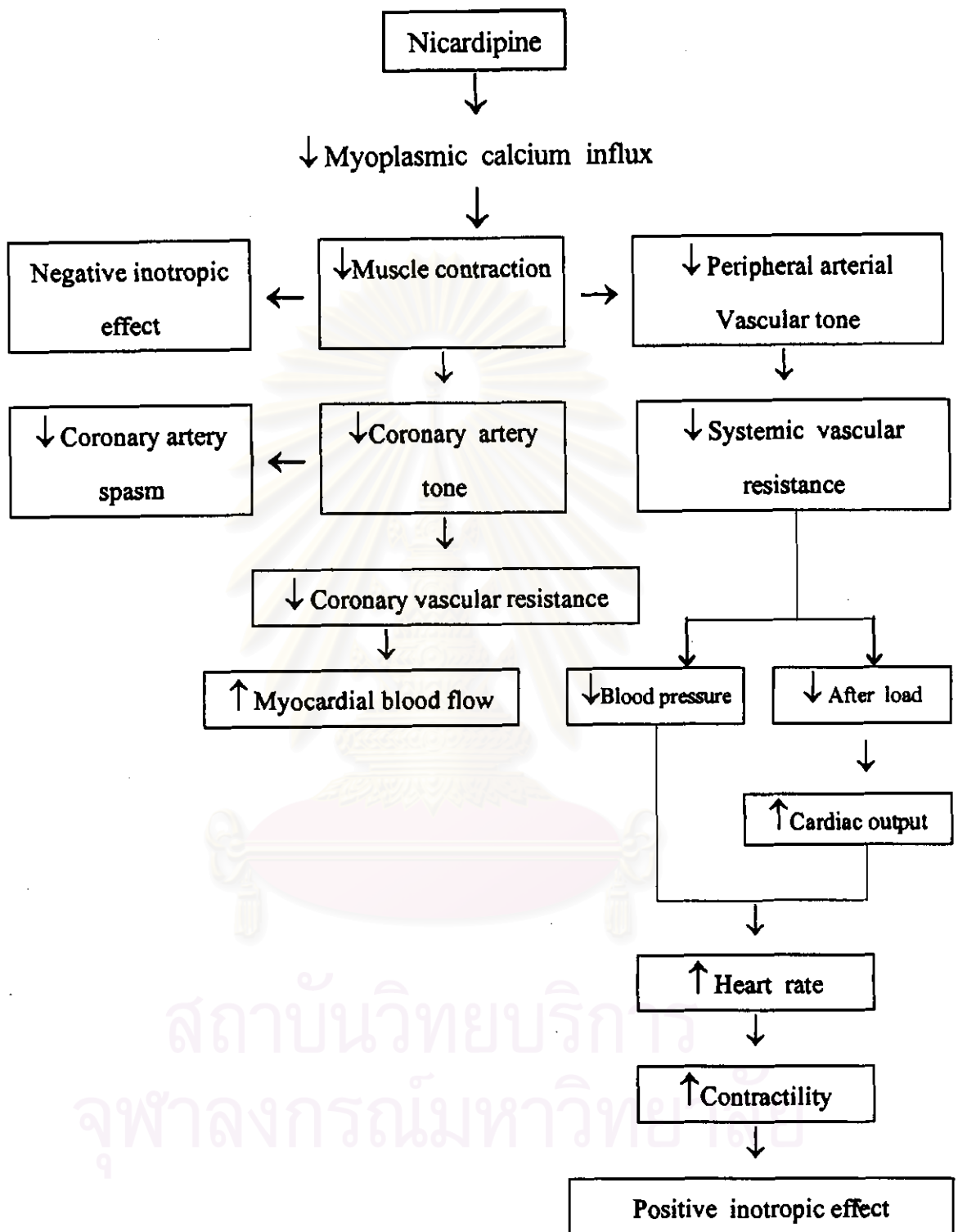
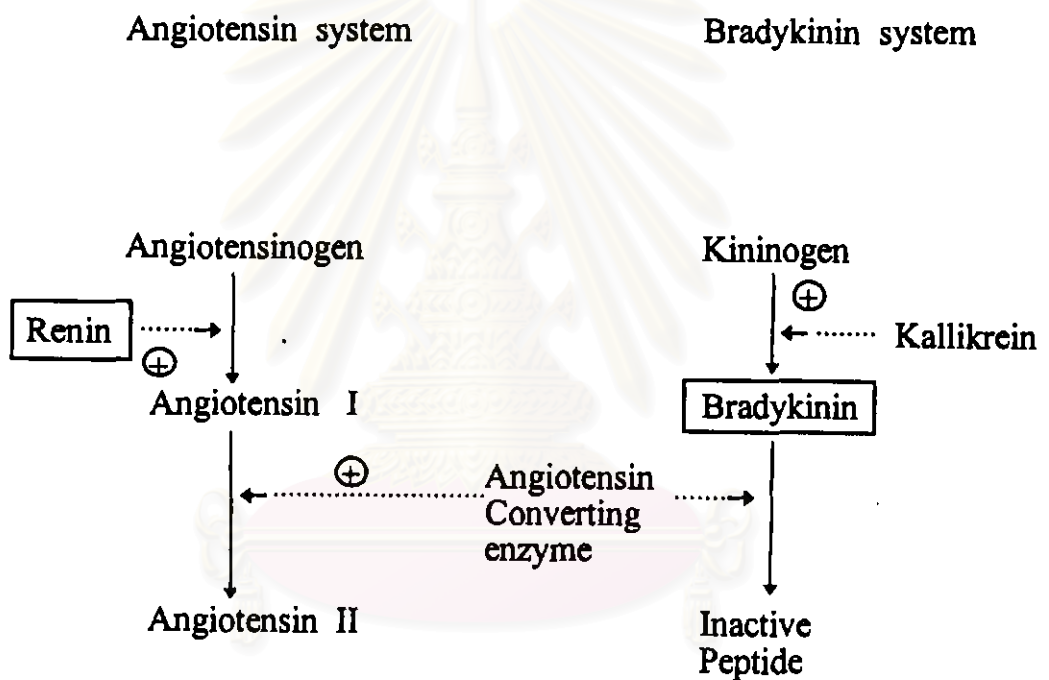


Figure 2.3 Effects of nicardipine on the myocardium and the coronary and peripheral arterial system ; \uparrow = increase ; \downarrow = decrease. (Lichtlen., 1984).



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Figure 2.4 Diagram of Renin - angiotensin system.

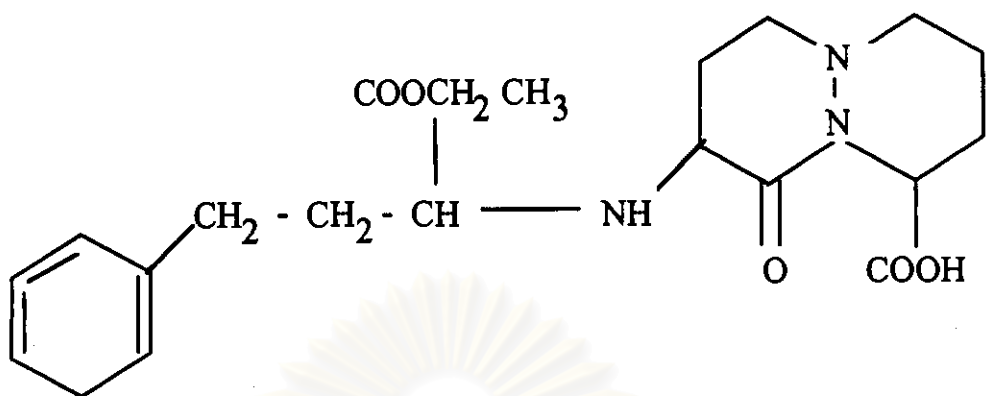
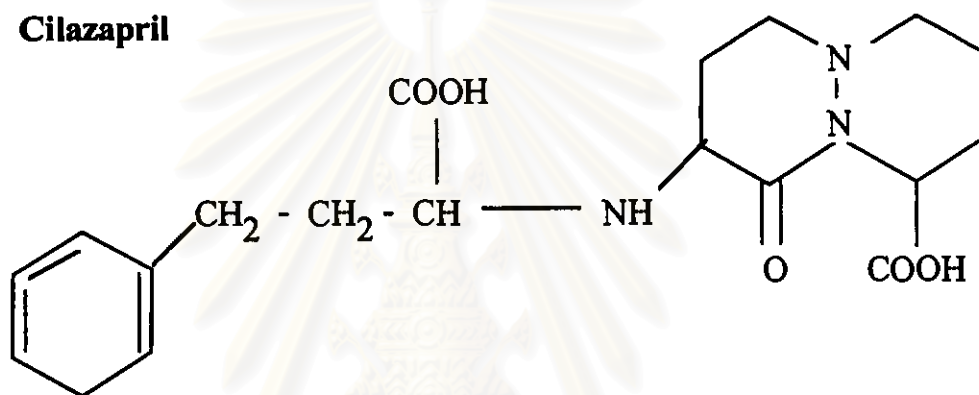
**Cilazapril****Cilazaprilat**

Figure 2.5 Structural formula of cilazaprilat, the active metabolite of cilazapril (Kleinbloesem et al., 1989).

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