CHAPTER IV

DISCUSSION AND CONCLUSION

The effect of capsaicin on isolated cardiac tissue preparations has received relatively little attention despite the known capacity of this chemical to induce profound alterations in cardiovascular performances when injected into whole animals. Although it is generally believed that most cardiovascular actions of capsaicin are reflex in nature, the possible contribution of direct action on cardiac and vascular tissues cannot be ignored. In fact, Molnar *et al.* (1969) and Fukuda and Fujiwara (1969) have independently demonstrated the positive chronotropic and inotropic effect induced by very low doses of capsaicin (0.5 µg/ml or less) on isolated guinea pig atria. This capsaicin-evoked cardiac stimulation was found insensitive to propranolol or reserpine pretreatment, indicating that the adrenergic mechanism is unlikely to involve. Toda and coworkers (1972) also demonstrated that capsaicin at 0.02 - 2.0 µg/ml caused sustained contraction of spiral strip from mesenteric and renal arteries of the dog. The tension increment was not significantly altered by phentolamine, suggesting the direct action of capsaicin on vascular tissue. In this thesis the action of capsaicin, with and without selected cardiac drugs, on the rate and isometric tension by isolated rat atria has been studied. The isolated right and left rat atria were used separately to investigate the effect of drugs on the rate and isometric force respectively. This technique eliminates the

possible interference between rate and contractile force observed with whole atria. Capsaicin at 0.2 to 10 µg/ml produces initial stimulation of right atrial rate and left atrial isometric force. The cardiac stimulation mediated by capsaicin is not blocked by propranolol or reserpine pretreatment. These results are similar to those obtained by Molnar *et al*. (1969) using isolated guinea pig atria. In addition, the present study also demonstrates that methysergide, a 5-HT antagonist, plus propranolol cannot abolish the cardiac-stimulating activity of capsaicin. Thus, these findings strongly indicate that capsaicin does not indirectly stimulate the atria by releasing intra-cardiac stores of catecholamines and serotonin. The latter can stimulate the heart by direct action on the myocardium and indirectly by releasing endogenous catecholamines (Higgins *et al*., 1981). Since capsaicin is known to be a substance P releaser (Buck and Burks, 1983), it remains to be investigated whether substance P participates in the positive chronotropy and inotropy induced by capsaicin. At present, reports on cardiovascular actions of substance P appear controversial. Some investigators have reported that substance P has minimal or no action on the heart; others have found substance P to increase cardiac work, cardiac output, heart rate, and coronary blood flow (see references quoted by Kulakowski *et al*., 1983). It is also worth mentioning that high dose of capsaicin (10 µg/ml) causes a clear depression, after acute stimulation, of both the rate and isometric force. The mechanism of this negative chronotropy is unclear but may be speculated to result from SA nodal membrane perturbation, inasmuch as capsaicin molecule contains the lipophilic acylamide group. On the other hand, inhibition of mitochondrial oxidative phosphorylation (Chudapongse and

Janthasoot, 1976) may be responsible for the capsaicin-induced negative inotropy.

Three cardiac drugs namely, propranolol, verapamil, and procainamide, have been selected for study with capsaicin. Propranolol is a non-selective β-antagonist which has been employed in the treatment of various cardiovascular diseases including hypertension, cardiac arrhythmias, and angina pectoris. Verapamil is a relatively new drug which belongs to the class of drug known as "calcium antagonists" (Fleckenstein, 1977). These drugs have only recently been employed clinically; and have been found particularly effective in the management of cardiac arrhythmias and angina pectoris (Singh *et al.*, 1980; Zsoter, 1980). The main therapeutic use of procainamide is as an antiarrhythmic agent. Of the three cardiac drugs studied, the clear and striking drug interaction has been observed between capsaicin and verapamil. The verapamil-induced negative chronotropy and inotropy is antagonized by capsaicin in a dose-dependent manner. The mechanism of this interesting drug interaction is at present a matter of conjecture. It is known that catecholamines effectively inhibit the depressive action of verapamil on the heart (Flekenstein, 1977). However, the antagonistic activity of capsaicin is not significantly modified by reserpine pretreatment,thus negates the involvement of endogenous catecholamine release. Also, the acute cardiac-stimulating action of capsaicin seems unlikely to involve since capsaicin can attenuate the effect of verapamil added after the capsaicin-evoked cardiac stimulation has declined. It has been proposed that verapamil as well as other calcium antagonists act by selective blockade of slow calcium channel and thereby inhibit calcium influx through

cardiac cell membrane (Fleckenstein, 1977). This proposal evidently implies the cell membrane as the site of verapamil action. Other investigators, however, favor the view that calcium antagonists act inside myocardial cell by inhibiting the release of calcium from various intracellular pools (Zsoter, 1980). Pang and Sperelakis (1983, 1984) have studied the uptake of verapamil and other calcium antagonists into cardiac, smooth and skeletal muscles. They found that these drugs were accumulated by the muscles; and the uptakes of these drugs were related to their lipid solubilities. They suggest that calcium antagonists particularly those having relatively high lipid solubilities, e.g., verapamil and bepridil, may have secondary site of aciton inside myocardial cells. Calcium antagonists are group of drugs having variable chemical structures (Zsoter, 1980); and it appears unlikely that they produce their effects by acting on common receptor. So far, there is no report concerning calcium antagonist receptor. Thus the precise mechanism of action of calcium antagonists remains to be elucidated. Since verapamil is relatively high lipid soluble (Pang and Sperelakis, 1984) and capsaicin molecule also contains the lipophilic acylamide side chain, the verapamil-capsaicin interaction may be speculated to result from the competition for the hydrophobic binding site(s) inside myocardial cell and/or at the cell membrane. This interaction is likely to be non-specific since procainamide, which is also lipid soluble, has similar antagonizing activity. Further experiments are needed to substantiate this point. It should be interesting to investigate whether other antiarrhythmic drugs such as quinidine, lidocaine, and diphenylhydantoin, which are lipid soluble to certain extent, have any effect on the cardiovascular

action of verapamil and other calcium antagonists.

In conclusion, capsaicin was found to mitigate the negative chronotropic and inotropic effects of verapamil on the isolated rat atria. It is suggested that competition for the cardiac hydrophobic regions is responsible for this drug interaction. The clinical significance of this interaction is not known at present. Nevertheless, the capacity of low dose of capsaicin (0.2 µg/ml) to alleviate verapamil action is sufficed to caution cardiac patients on verapamil therapy against consumption of foods containing hot pepper in large amount.