DISCUSSION

The results demonstrated that all catecholamines used in the present study significantly altered in the responsiveness of cardiac β-adrenoceptors both in the isolated rat atrial preparations and anesthetized rats during the development of morphine dependence and morphine withdrawal. The increase and decrease of heart rate and/or contractile force (tension) both *in vitro* and *in vivo* during the development of morphine dependence and morphine withdrawal, respectively is mainly mediated via β_1-adrenoceptors. These evidences seemed to support a corresponding up-regulation and down-regulation of cardiac β-adrenoceptors in morphine-dependent and morphine-withdrawal rats, respectively in the peripheral nervous system as similar to those occurred in brain as reported previously (Kuriyama *et al.* 1981, Llorens *et al.* 1978, Moises & Smith 1985; 1987). The explanation for why the alterations in responsiveness of cardiac β-adrenoceptors to catecholamines during the development of morphine dependence and morphine withdrawal may be due to a prolonged exposure of cardiac β-adrenoceptors to morphine treatment.

A recent functional study has been made in an attempt to support that prolonged treatment with β-adrenoceptor antagonists and agonists could alter in responsiveness of β-adrenoceptors to some exogenous agonists *in vitro* (Chang & Einstein 1996, Hauck *et al.* 1997). In some studies, there was evidence that even short-term exposure to β-adrenoceptor agonists can lead to phosphorylation of β-adrenoceptors and to alterations in the β-receptor-G-protein complex (Roth *et al.* 1991) with uncoupling of β-adrenoceptors from the stimulant G-protein (Pitcher *et al.* 1992). However,the changes in responses of any cell or organ to sympathomimetic amines are depended on an adrenoceptor density, proportion of α- and β-adrenergic receptors, duration of exposure and diseased conditions. Jakob *et al.* 1995 has shown that treatment with captopril for 2-3 months upregulates β-adrenoceptors and induces a trend towards downregulation of $G_{i\alpha}$-proteins in endomyocardial biopsies from patients with mild to moderate heart failure (NYHA class II-III). It is now well established that there are at least three subtypes of β-adrenoceptors, β_1-, β_2- and β_3-adrenoceptors (Arch *et al.* 1984, Emorine *et al.* 1989, Lefkowitz *et al.* 1991). The increase and decrease of responsiveness to norepinephrine in chronic morphine-treated and morphine-withdrawal rats may be explained on the basis of the adrenoceptor subtypes in the isolated rat atria. Generally, norepinephrine is one of the most potent vasoconstrictor agents, and the effects of continuous intravenous infusion of norepinephrine on the cardiovascular system have been well documented (Allwood et al. 1963, Goldberg et al. 1950). Norepinephrine is not only an agonist of the α-adrenoceptors but also of β-adrenoceptors. Norepinephrine infusion induces an inotropic effect via β_1-adrenoceptors and a marked increase in blood pressure, mediated via α-adrenoceptors.

Since β_1-subtype is almost absolutely located at the myocardium, therefore, the possibility of increase or decrease in the affinity and/or number of cardiac β_1-adrenoceptors in chronic morphine-treated and morphine-withdrawal rats may be responsible for the alterations in responsiveness to catecholamines. Butterfield & Chess-William (1993) reported that norepinephrine (1 mg kg^{-1}) or isoproterenol (40 $\mu g\ kg^{-1}$) infused for 3 days resulted in a desensitization of β-adrenoceptors-mediated responses of isolated left atria and papillary muscles. The present findings of our study could suggest that the sensitivity of cardiac β_1-adrenoceptors to epinephrine, isoproterenol and dopamine in chronic morphine-treated and morphine-withdrawal isolated rat atria and anesthetized rats compared with saline-treated rats was likely to alter. Epinephrine, isoproterenol and dopamine had a marked action on cardiac β_1-adrenoceptors which were accounted for changing in the affinity and/or number of receptors during the development of morphine dependence and morphine withdrawal. It has been well documented that epinephrine is a potent stimulator of α- and β-adrenoceptors and it acts directly on the predominant β_1 receptors of the myocardium and of the cells of the pacemaker and conducting tissues while isoproterenol is a potent nonselective β-adrenergic agonist, producing inotropic and chronotropic effects via both β_1- and β_2-adrenoceptors with very low affinity for α-adrenergic receptors. Consequently, isoproterenol has a powerful effects on all β receptors and almost no action at α receptors. Dopamine at low conentrations acts at vascular D_1-dopaminergic receptors, especially in the renal, mesenteric, and coronary beds while at somewhat higher concentrations dopamine exerts a positive inotropic effect on the myocardium, acting via β_1-adrenergic receptors. The rank order of

potency of catecholamines is isoproterenol > epinephrine ≥ norepinephrine for β and epinephrine ≥ norepinephrine >> isoproterenol for α (Lefkowitz *et al.* 1991). β-Adrenergic agonists that activate β- adrenoceptors may be used to stimulate the rate and force of cardiac contraction. The results of the present investigation, concerning sensitivity of cardiac β-adrenoceptors of isolated rat atrial preparations and anethetized rats to catecholamines, are also related with the findings of a recent study in the another preparation which showed that pretreatment of human bronchi with β-adrenoceptor agonists leads to functional desensitization and, in lung tissue, to down-regulation of β-adrenoceptors and this effect can be counteracted by additional administration of dexamethasone (Hauck *et al.* 1997). Chronic morphine treatment and morphine withdrawal caused a slight increase and decrease, respectively in the responsiveness of cardiac β-adrenoceptors when the results were compared with those from the control group. These indicated that any changes in the responses to β-adrenoceptor agonists were unlikely to result from some non-specific changes in responsiveness and were mostly likely to be due to receptor-specific regulatory mechanisms (Chang & Einstein 1996).

In summary, the present investigation revealed that the responsiveness of β-adrenoceptor to catecholamines (heart rate and tension) in morphine-dependent and morphine-withdrawal rats are likely to increase and decrease, respectively. These results could be assumed that an up-regulation and down-regulation of cardiac β_1-adrenoceptors in chronic morphine-treated and morphine-withdrawal rats as the similar way to those occurring in the central nervous system. These findings may have important clinical implications for the rational use of β-adrenoceptor agonists in the morphine-dependent and morphine-withdrawal conditions.