

## Mechanism of Decrease in Heart Rate by Peripheral Dopaminergic D<sub>2</sub>-Receptors

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*We performed this study in order to verify the heart rate decrease caused by the D<sub>2</sub>-receptor on cardiac sympathetic nerve endings and its relation to the concentration of norepinephrine in synaptic clefts. Sprague-Dawley rats were pithed and the heart rate was increased either by electrical stimulation of the cardiac accelerator nerve or by intravenous infusion of norepinephrine, tyramine, or isoproterenol. Increased heart rate by electrical stimulation of cardiac accelerator nerve was dose-dependently lowered by lisuride and its effect was blocked by pretreatment with sulpiride but not with yohimbine and SCH 23390. Also, the heart rate was decreased in a dose-dependent manner by clonidine and this effect was blocked by pretreatment with yohimbine, but not with sulpiride. For increased heart rate by infusion of norepinephrine, tyramine, or isoproterenol, the heart rate lowering effect of lisuride was more marked in the norepinephrine- and tyramine-infusion groups, in which the intrasynaptic concentration of norepinephrine was elevated, compared to the isoproterenol-infusion group, in which intrasynaptic concentration of norepinephrine was not elevated. In conclusion, there is a D<sub>2</sub>-receptor on the cardiac sympathetic nerve endings which decreases the heart rate and is different from the presynaptic  $\alpha_2$ -receptor. Also, the heart rate lowering effect via stimulation of the D<sub>2</sub>-receptor by lisuride was more marked with increased concentration of norepinephrine in the synaptic cleft.*

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**Key Words:** Pithed rat, decrease in heart rate, D<sub>2</sub>-receptor, intrasynaptic concentration of norepinephrine

Dopamine, a naturally occurring catecholamine and the immediate precursor of norepinephrine, was first synthesized in 1910. Initial-

ly, dopamine was thought to be similar to epinephrine and norepinephrine in its effects. However, it was demonstrated that the action of dopamine is different from other catecholamines (Holtz and Credner, 1942). Peripheral dopaminergic receptors are present principally in renal and mesenteric vessels and also exist in coronary, cerebral, hepatic, and femoral vascular beds (Goldberg, 1972; McCulloch and Haper, 1977; Richardson and Withrington, 1977; Bell and Stubbs, 1978). Two classes of dopamine receptors, D<sub>1</sub> and D<sub>2</sub>, have been identified by biochemical and pharmacological criteria in the CNS. The D<sub>1</sub>-receptor was defined by its ability to stimulate adenylate cyclase,

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Received June 15, 1994

Accepted September 15, 1994

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This study was supported in part by the Yonsei University Research Grant (1993).

whereas the  $D_2$ -receptor was supposed not to activate this enzyme (Kebabian and Calne, 1979). Peripheral dopamine receptors have been indirectly identified by physiological methods. On the basis of agonist and antagonist potency and selectivity, there have been two classes, which have been named  $DA_1$  and  $DA_2$  by analogy but are not identical with the central  $D_1$ - and  $D_2$ -receptors (Goldberg and Kohli, 1979; Goldberg and Kohli, 1983).

It was well known that dopamine produces  $D_1$ -receptor mediated vasodilation (Goldberg, 1972) and also potentiates the vasodilation through  $D_2$ -receptor mediated inhibition of norepinephrine released from sympathetic nerve terminals (Lokhandwala and Barret, 1982; Eisinger *et al.* 1985). These effects of dopamine are important in the modulation of peripheral vascular resistance in terms of blood pressure control. Furthermore, it could have a certain role in the pathogenesis of hypertension and its management (Kuchel and Kuchel, 1991). There are experimental reports that dopamine depresses the cardiac functions through the inhibition of catecholamine release via stimulation of  $D_2$ -receptors in addition to postsynaptic  $D_1$ -receptor mediated vasodilation (Long *et al.* 1975; Fuder and Muscholl, 1978; Verplanken *et al.* 1983; Ko and Hong; 1988). In isolated rabbit atria, dopamine and apomorphine inhibit the chronotropic responses to electrical stimulation of the sympathetic nerves (Verplanken *et al.* 1983) and Dallas *et al.* (1986) reported that dopamine and DPDA (di-N-propyl dopamine) cause the decrease of heart rate which was increased by electrical stimulation of the cardiac accelerator nerves in *in vivo* cat. Also, Ko and Hong (1987) demonstrated that dopamine and other  $D_2$ -receptor agonists, such as lisuride, bromocriptine, and apomorphine cause the decrease in heart rate under pretreatment of desipramine, which inhibits the reuptake of norepinephrine in sympathetic nerve terminals.

However, administration of dopamine caused the elevation of blood pressure and tachycardia through the stimulation of sympathetic  $\alpha$ - and  $\beta$ -receptors instead of cardiovascular depression (Goldberg, 1972). Also, considering the fact that it was necessary to increase the

heart rate by electrical stimulation or pretreatment with cocaine or desipramine for the demonstration of cardiovascular depression by peripheral dopaminergic receptors (Fuder and Muscholl, 1978; Verplanken *et al.* 1983; Ko and Hong; 1988), we hypothesized that the increased norepinephrine concentration in the synaptic cleft might be required for elicitation of cardiovascular depression through dopaminergic receptors.

We performed this study to verify the decrease in heart rate by the  $D_2$ -receptor on cardiac sympathetic nerve endings and its relation to the concentration of norepinephrine in synaptic clefts using pithed Sprague-Dawley rats.

## METHODS

### Preparation of experimental animals

Sprague-Dawley rats of either sex weighing 180 to 220 gm were used. Rats were anesthetized with sodium pentobarbital, approximately 50 mg/kg *i.p.* The trachea was cannulated and ventilation was artificially maintained with 100%  $O_2$  via tracheal cannula attached to the Narco Ventilator (Houston, Texas, USA). An intravenous line was kept at the tail vein by vinca tube for drug administration. Atropine sulfate, 2 mg, was given subcutaneously. Bilateral vagotomy was performed to prevent the reflex change of the heart rate. Blood pressure was recorded via right carotid artery attached to the pressure transducer and heart rate was derived from the blood pressure pulse using a tachographic preamplifier. Rectal temperature was kept at about 37°C with a heating jacket and light throughout the experiment. The rats were pithed by introducing a blunt steel rod into the spinal canal via the right orbit. Thereafter, the pithing rod was rapidly replaced by a partially insulated electrode and positioned at the level of  $C_7-T_1$  for anodal electrical stimulation using the method by Gillespie and Muir (1967). An indifferent electrode was placed subcutaneously in the neck. Pancuronium bromide (0.2 mg) was given intravenously

to prevent muscle twitching due to electrical stimulation of the cardiac accelerator nerve.

#### Heart rate increase by electrical stimulation of cardiac accelerator nerve

The pithed rat was electrically stimulated by pithing electrode as an anode and an indifferent electrode as a cathode positioned subcutaneously at posterior neck. Electrical stimulation was performed by monophasic square wave pulses (3Hz, 50ms in duration) and the position of the pithing electrode was adjusted to increase the heart rate by 100 beats/min with little change in the blood pressure.

#### Effects of lisuride or clonidine on heart rate in pithed, electrically stimulated rats pretreated with or without various D<sub>2</sub>, D<sub>1</sub>, or $\alpha_2$ -antagonists

Lisuride was used to investigate the existence of D<sub>2</sub>-receptors in sympathetic nerve terminals probably mediating the decrease of the heart rate. Lisuride (100, 300, 560, 1000  $\mu$ g/kg) was infused intravenously for 1 minute starting 25 minutes after pretreatment with or without sulpiride (10 mg/kg or 30 mg/kg), yohimbine (5 mg/kg), or SCH 23390 (10 mg/kg). In other experiments, clonidine (0.1, 1, 10, 100, 1000, 3000  $\mu$ g/kg) was infused for 1 minute to evaluate the involvement of the presynaptic  $\alpha_2$ -receptor in the heart rate lowering effect with or without pretreatment with sulpiride or yohimbine.

#### Heart rate increase by continuous infusion of norepinephrine, tyramine, or isoproterenol

After pithing, norepinephrine, tyramine, or isoproterenol was infused continuously using infusion pump (HM-6000, Hanseung Electronics, Korea) via the left internal jugular vein. The infusion rate was adjusted to increase the heart rate by 100 beats/min or more. The infusion rate was 13  $\mu$ g/kg/min for norepinephrine, 33  $\mu$ g/kg/min for tyramine, and 1.3  $\mu$ g/kg/min for isoproterenol. After the heart rate was stabilized, lisuride was administered by the injection method stated above to evaluate the heart rate lowering effect via

the D<sub>2</sub>-receptor under the different intrasynaptic concentrations of norepinephrine.

#### Drugs

The following drugs were used in this experiments: Lisuride hydrogen maleate (Research Biochemical Incorporation, Natick, MA, USA), ( $\pm$ )-sulpiride (Sigma Chemical Co, St. Louis, MO, USA), yohimbine (Sigma Chemical Co, St. Louis, MO, USA), clonidine (Sigma Chemical Co, St. Louis, MO, USA), SCH 23390 (Research Biochemical Incorporation, Natick, MA, USA), SK&F 38393 (Research Biochemical Incorporation, Natick, MA, USA), atropine sulfate (Sigma Chemical Co, St. Louis, MO, USA), pancuronium bromide (Iyeon Pharma Co, Korea), isoproterenol (Sigma Chemical Co, St. Louis, MO, USA), tyramine (Sigma Chemical Co, St. Louis, MO, USA), and norepinephrine (Sigma Chemical Co, St. Louis, MO, USA).

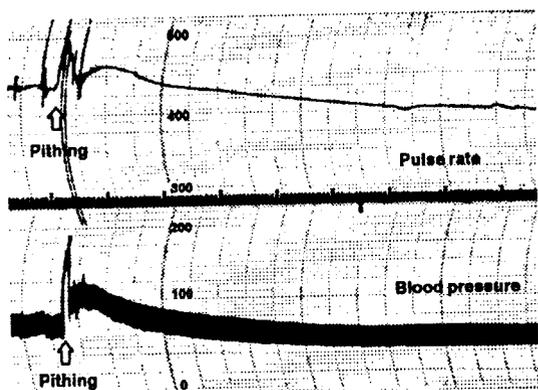
Lisuride was dissolved in 10<sup>-3</sup>N HCl and other drugs were dissolved with D/W.

#### Analysis of results

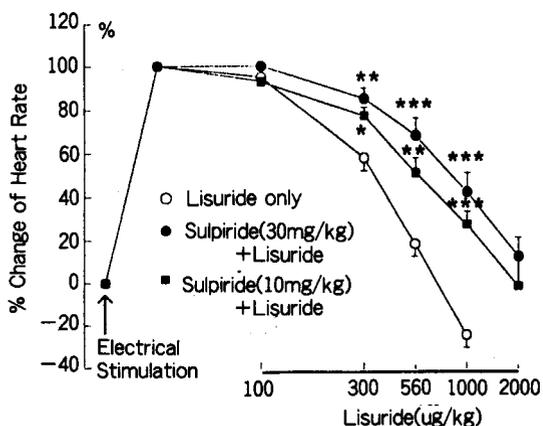
Defining as 0% of resting heart rate after pithing and 100% of increased heart rate by electrical stimulation or drug infusion, changes in heart rate by drug administration were expressed as % change of heart rate. Results were expressed as mean  $\pm$  SEM. Student's test was used for comparison between the agonist-induced effect and the antagonist effect on the agonist. P value less than 0.05 was considered to indicate a significant difference.

## RESULTS

The heart rate was 350  $\pm$  5 beats/min at resting state after the pithing procedure. Seven to ten volts were required for increasing the heart rate by 100 beats/min or more with electrical stimulation of the cardiac accelerator nerve (Fig. 1). Increased heart rate was maintained about 30 minutes at least. Heart rate response to the solvent, 10<sup>-3</sup>N HCl, was meager in effect after repeated admini-



**Fig. 1.** Change of heart rate and blood pressure during pithing. At the time of pithing, heart rate and blood pressure were abruptly elevated and stabilized after about 25 min. Pithed heart rate was  $350 \pm 5$  beats/min and 7 to 10 volts was required for increasing the heart rate of 100 beats/min or more by electrical stimulation of cardiac accelerator nerve.



**Fig. 2.** Effect of sulpiride pretreatment on the heart rate decrease by lisuride in pithed rats in which heart rate was increased by electrical stimulation of cardiac accelerator nerve. Heart lowering effect of lisuride was blocked by sulpiride pretreatment. \*:  $p < 0.05$ , \*\*:  $p < 0.01$ , \*\*\*:  $p < 0.001$ ; Lisuride only vs. lisuride after sulpiride. Data are expressed as mean  $\pm$  SEM of 6 rats per group.

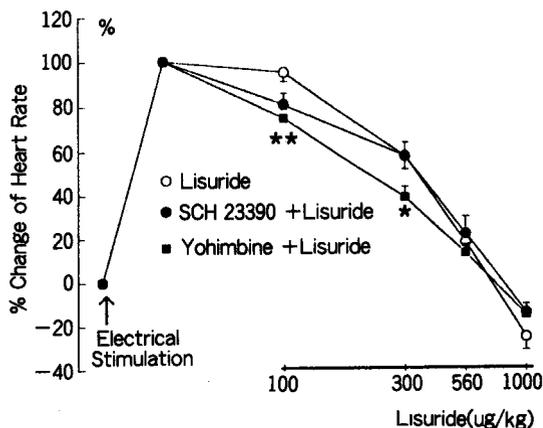
stration.

**Effect of sulpiride, SCH 23390 or yohimbine on heart rate lowering effect of lisuride**

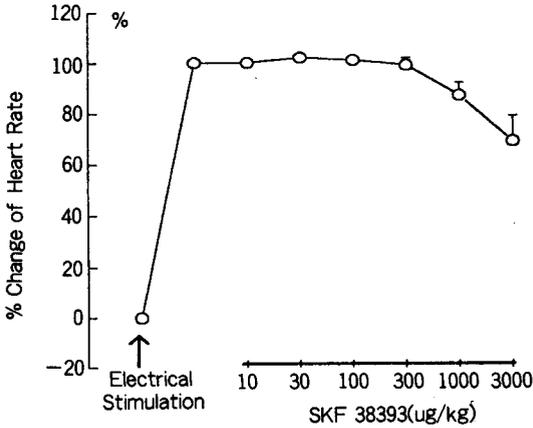
In electrically stimulated pithed rats, lisuride (100, 300, 560, 1000  $\mu$ g/kg i.v.) produced a dose-dependent decrease in heart rate (Fig. 2). This effect was attained 3 minutes after the administration of lisuride. At a dose of 1000  $\mu$ g/kg of lisuride, the heart rate was decreased down to the level of the pithed state. This effect was antagonised by sulpiride (10 mg/kg and 30 mg/kg). The dose-response curve to lisuride was shifted to the right. However, the heart rate lowering effect of lisuride was not antagonized by pretreatment with SCH 23390 or yohimbine (Fig. 3). These heart rate lowering effect of SK&F 38393 was meager at lower dosages but prominent at higher dosages (more than 300  $\mu$ g/kg) (Fig. 4).

**Effect of sulpiride or yohimbine on the heart rate lowering effect of clonidine**

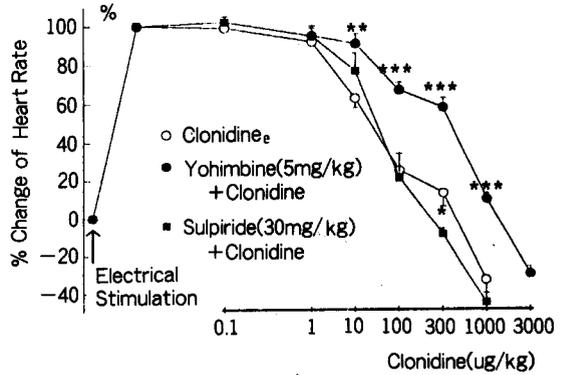
Clonidine decreased the heart rate dose-de-



**Fig. 3.** Effect of yohimbine or SCH 23390 pretreatment on the heart rate decrease by lisuride in pithed rats in which heart rate was increased by electrical stimulation of cardiac accelerator nerve. Heart lowering effect of lisuride was not blocked by yohimbine or SCH 23390 pretreatment. \*:  $p < 0.05$ , \*\*:  $p < 0.01$ ; Lisuride only vs. lisuride after yohimbine or SCH 23390. Data are expressed as mean  $\pm$  SEM of 6 rats per group.



**Fig. 4.** Effect of SK&F 38393 on the heart rate increased by electrical stimulation of cardiac accelerator nerve. SK&F at high concentration more than 300  $\mu\text{g}/\text{kg}$  decreased the heart rate. Data are expressed as mean  $\pm$  SEM of 6 rats per group.

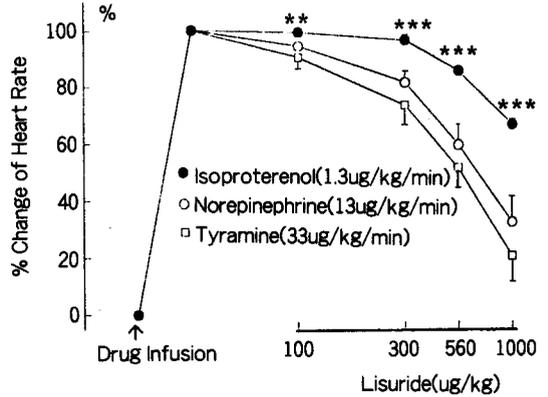


**Fig. 5.** Effect of sulpiride or yohimbine pretreatment on the heart rate decrease by clonidine in pithed rats in which heart rate was increased by electrical stimulation of cardiac accelerator nerve. Heart lowering effect of clonidine was blocked only by yohimbine pretreatment not by sulpiride pretreatment. \*:  $p < 0.05$ , \*\*:  $p < 0.01$ , \*\*\*:  $p < 0.001$ ; Clonidine only vs. clonidine after sulpiride. Data are expressed as mean  $\pm$  SEM of 6 rats per group.

pendently. At a dose of 1000  $\mu\text{g}/\text{kg}$  of clonidine, the heart rate was decreased down to the level of the pithed state. This effect was blocked by yohimbine pretreatment (5 mg/kg), so the dose-response curve to clonidine was shifted to the right. Sulpiride (30 mg/kg) had no effect on the heart rate decreased by clonidine (Fig. 5).

**Heart rate lowering effect of lisuride to heart rate increased by drug infusion**

Lisuride dose-dependently decreased the heart rate which was increased by norepinephrine and tyramine infusion. The % change of heart rate was  $94 \pm 1\%$  and  $90 \pm 4\%$  at 100  $\mu\text{g}/\text{kg}$  of lisuride,  $81 \pm 4\%$  and  $73 \pm 7\%$  at 300  $\mu\text{g}/\text{kg}$  of lisuride,  $59 \pm 7\%$  and  $51 \pm 7\%$  at 569  $\mu\text{g}/\text{kg}$  of lisuride, and  $32 \pm 9\%$  and  $20 \pm 9\%$  at 1000  $\mu\text{g}/\text{kg}$  of lisuride in both norepinephrine- and tyramine-infusion groups, respectively. In the isoproterenol-infusion group, the heart rate was decreased to  $99 \pm 0\%$ ,  $96 \pm 1\%$ ,  $83 \pm 3\%$ , and  $50 \pm 7\%$  with the administration of equivalent dosages of lisuride. Therefore, the heart rate lowering effect of lisuride was more marked



**Fig. 6.** Effect on the heart rate decrease by lisuride in pithed rats in which heart rate was increased by infusion of norepinephrine, tyramine or isoproterenol. Heart lowering effect of lisuride was marked in norepinephrine- or tyramine-infusion group than isoproterenol-infusion group. \*:  $p < 0.05$ , \*\*:  $p < 0.01$ , \*\*\*:  $p < 0.001$ ; Norepinephrine- or tyramine-infusion group vs isoproterenol-infusion group. Data are expressed as mean  $\pm$  SEM of 6 rats per group.

in norepinephrine- and tyramine-infused rats compared to isoproterenol-infused rats (Fig. 6).

## DISCUSSION

It has been well known that there is a presynaptic dopaminergic receptor inhibiting the release of norepinephrine from the sympathetic nerve terminals in addition to the presynaptic  $\alpha_2$ -receptor (Enero and Langer, 1975; Langer and Dubocovich, 1979; Dubocovich and Langer, 1980; Langer *et al.* 1980; Massingham *et al.* 1980; Buylaert *et al.* 1981; Langer, 1981). Langer (1973) reported in the first that exogenous dopamine caused inhibition of  $^3\text{H}$ -noradrenaline release in the perfused spleen. In the experiment that exogenous dopamine inhibited norepinephrine release and this effect was blocked by dopamine antagonist, McCulloch *et al.* (1973) insisted that this effect is via dopaminergic receptor (Enero and Langer, 1975; Hope *et al.* 1978).

There is some evidence that there are presynaptic  $D_2$ -receptors inhibiting norepinephrine release from sympathetic nerve terminals in the heart, and that the heart rate is decreased via  $D_2$ -receptors. Fuder and Muscholl (1978) reported in perfused rabbit heart that exogenous dopamine inhibited norepinephrine release caused by electrical stimulation of the cardiac accelerator nerves under the pretreatment of cocaine, and this effect was blocked by a dopaminergic antagonist. Verplanken *et al.* (1983) presented that heart rate decrease by dopamine or dopaminergic agonist occurred via presynaptic  $D_2$ -receptors, in which the heart rate decrease by dopamine or dopaminergic agonist was blocked only by  $D_2$ -antagonist, not by  $\alpha_2$ -antagonist. Therefore, heart rate decrease by dopamine or dopaminergic agonist was caused by inhibition of norepinephrine release via presynaptic  $D_2$ -receptors (Fuder and Muscholl, 1978; Cavero *et al.* 1982; Ko and Hong, 1987). Wilffert *et al.* (1984), however, had an contrary view that rat sympathetic nerves do not contain inhibitory dopamine receptors and the heart rate lowering effect by the dopaminergic agonist was medi-

ated by presynaptic  $\alpha_2$ -receptor stimulation. In the present study, heart rate, which was increased by electrical stimulation of cardiac accelerator nerve in pithed rat, was dose-dependently decreased by lisuride and its effect was blocked by pretreatment with sulpiride, but not by pretreatment with yohimbine or SCH 23390. Heart rate was dose-dependently decreased by clonidine and this effect was blocked by pretreatment with yohimbine, but not with sulpiride. Our results confirm earlier findings that there are  $D_2$ -receptors, which decrease the heart rate and are different from presynaptic  $\alpha_2$ -receptor, on the cardiac sympathetic nerve endings (Cavero *et al.* 1982; Willems *et al.* 1985; Ko and Hong, 1987). SK&F 38393 caused the decrease in heart rate, which is derived from the inhibition of neurotransmission via  $D_1$ -receptor stimulation (Grega *et al.* 1984), at a high dose of more than 300  $\mu\text{g}/\text{kg}$ .

In this study, it is interesting to note that lisuride depresses the heart rate more markedly in the norepinephrine- or tyramine-infusion groups than the isoproterenol-infusion group. Exogenous norepinephrine comes into the synaptic cleft by simple diffusion, whereas tyramine releases norepinephrine from sympathetic nerve terminals by displacing norepinephrine in the cytoplasm of terminal neurons (Gilmann *et al.* 1991). Both of these drugs cause an increase in the heart rate by increasing the intrasynaptic concentration of norepinephrine, which stimulates the postsynaptic  $\beta_1$ -receptor in synaptic clefts. In contrast, isoproterenol increases the heart rate by directly stimulating the  $\beta_1$ -receptor without an increase of the intrasynaptic concentration of norepinephrine. For the heart rate increased by different mechanisms, lisuride caused more prominent effect on the heart rate decrease in norepinephrine- or tyramine-infusion groups, in which the intrasynaptic concentration of norepinephrine was increased, than the isoproterenol infusion group, in which concentration of intrasynaptic norepinephrine was not elevated. Therefore this result suggests that the heart rate lowering effect via  $D_2$ -receptor is closely related to the intrasynaptic concentration of norepinephrine. Taking into considera-

tion of these results and need of increasing the heart rate by electrical stimulation or pretreatment with cocaine or desipramine in order to demonstrate the cardiovascular depression by peripheral dopaminergic receptors in the past reports (Fuder and Muscholl, 1978; Ko and Hong, 1987), it is thought that increased intrasynaptic concentration of norepinephrine was necessary to elicit the cardiac inhibition. However, the present study is limited concerning the explanation of the mechanism of heightened decrease in heart rate by lisuride in the increased concentration of norepinephrine in the synaptic cleft. It might be necessary to clarify this unexplained result in the next study.

The heart rate lowering effect by lisuride was also noted in the isoproterenol-infusion group as well as in the norepinephrine- or tyramine-infusion groups. This results suggest the possibility of another mechanism in heart rate decrease via D<sub>2</sub>-receptor in addition to the presynaptic mechanism of norepinephrine release from sympathetic nerve terminals. Because the sympathetic  $\beta_1$ -receptor is coupled to adenylate cyclase and its stimulation increases the intracellular cyclic AMP level, and the stimulation of D<sub>2</sub>-receptor decreases intracellular cyclic AMP level (Kebabian and Calne, 1979; Missale *et al.* 1988), it might be conjectured that intracellular biochemical alterations by D<sub>2</sub>-receptor stimulation may be intervened in this heart rate decrease in isoproterenol-infusion group as well as norepinephrine- or tyramine-infusion group. Currently, there is no known evidence about intracellular alterations in myocardium via D<sub>2</sub>-receptors or the presence of D<sub>2</sub>-receptors on the myocardium itself except Sandrini's report (1986).

The present results suggest that there is a D<sub>2</sub>-receptor on the cardiac sympathetic nerve endings which decreases the heart rate and is different from presynaptic  $\alpha_2$ -receptor, and that the heart rate lowering effect via stimulation of the D<sub>2</sub>-receptor was more marked with an increased concentration of norepinephrine in the synaptic cleft.

## ACKNOWLEDGEMENTS

The technical assistance of Mr. Seo Sang-Gun and Miss Choi Hong-Soon is gratefully acknowledged.

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## Peripheral Dopaminergic D<sub>2</sub>-Receptor

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