Effect of Chronic Administration of Denopamine (TA-064), a New Positive Inotropic Agent, on Cardiac Response of Rats to Denopamine

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Abstract—Effects of chronic administration of denopamine on acute cardiovascular response to denopamine were studied in anesthetized rats. Effects of repeated treatment with isoproterenol was also investigated. The dose of denopamine to increase LV dp/dt max by 50% of the control (ED50) was 0.77 mg/kg, p.o. Following chronic administration of denopamine once daily at 10 or 20 mg/kg, p.o., for 14 days, the effect of denopamine (i.v.) on LV dp/dt max was similar to that in the control group. In the 40 mg/kg-group, however, the positive inotropic effect of denopamine (i.v.) was attenuated significantly at lower doses without a decrease in the maximal response and the ED50 was increased 1.8-fold. Chronic treatment with denopamine in the diet at 20 or 40 mg/kg/day for 14 days did not influence the response to the drug. By subcutaneous administration of 50 μg/kg isoproterenol, thrice daily for 3 days, the ED50 of isoproterenol (i.v.) for positive inotropy were increased 6.8-fold. In addition, the maximal response to isoproterenol was depressed to about 70% of that obtained in the control. In the preparation desensitized by isoproterenol (50 μg/kg), the inotropic response to denopamine was attenuated at lower doses, but the maximal response was not altered. In the groups desensitized by the two drugs, the positive chronotropic effect of the drugs (i.v.) tended to decrease and the effects on blood pressure was not changed. By Scatchard analysis, the specific 3H-dihydroalprenolol binding to the cardiac membranes (Bmax) was reduced in the 40 mg/kg denopamine (p.o.) group as well as in the isoproterenol-treated groups. In the 10 mg/kg denopamine and 20 mg/kg denopamine groups, however, Bmax was not changed. These results suggest that chronic administration of denopamine hardly results in desensitization of its positive inotropy at the effective doses.

Denopamine is an orally active, positive inotropic agent with modest effect on heart rate, and it has a highly selective β1-adrenoceptor agonistic property (1). Several β-adrenoceptor agents such as dobutamine (2) and pirbuterol (3) have been shown to cause the development of tolerance to the hemodynamic effect after continuous administration for 3–7 days in humans. Prolonged in vivo infusion of isoproterenol for 4 days has been reported to cause a shift in the dose-response curves (4) and a decrease in the maximal response (5) to isoproterenol. Furthermore, it has been shown that isoproterenol causes desensitization of its positive inotropy and adenylate cyclase activity, accompanied by down-regulation of β-adrenoceptors and/or with uncoupling of the receptor-adenylate cyclase complex (6–11).

We have investigated whether denopamine promotes desensitization of its positive inotropy in vivo and down-regulation of β-adrenoceptors following chronic administration of denopamine to rats. Alteration in cardiac sensitivity to isoproterenol after
repeated administration was also investigated.

**Materials and Methods**

**Animals:** Male Sprague-Dawley rats of 5–8 weeks of age (Charles River Japan Inc.) were used in the present experiment.

**Inotropic effects of denopamine and isoproterenol in anesthetized rats:** Animals were anesthetized with pentobarbital sodium (50 mg/kg, i.p.). Left ventricular pressure was measured with a high-fidelity pressure transducer (Century Technology Company, CP-01). The transducer was connected to an injection needle with polyethylene tubing, inserted into the ventricle through the left sixth or seventh intercostal space. The first derivative of left ventricular pressure (LV dp/dt) was obtained with an analogue differentiator amplifier (Nihon Kohden, ED-601G, time constant of 0.5 msec). Blood pressure was measured with a pressure transducer (Nihon Kohden, MPU-0.5) which was connected to polyethylene tubing inserted into the femoral artery. Heart rate was measured by means of a cardiograph (Nihon Kohden, AT-601G), triggered by the arterial pressure pulse. All the measurements were recorded on a recorder (Nihon Kohden, WT-685G).

A cannula was inserted in advance into the stomach through the mouth or into the femoral vein. Denopamine was administered into the stomach (i.g.) through the inserted cannula. Isoproterenol was injected intravenously (i.v.) or subcutaneously (s.c.). Denopamine was suspended in 0.25% carboxymethyl cellulose (CMC) aqueous solution for chronic administration. Isoproterenol was dissolved in 0.9% NaCl solution.

**Chronic treatment with denopamine:** In the preliminary experiment, oral administration of 1–30 mg/kg denopamine for 7 days did not induce desensitization of cardiovascular response to denopamine. Accordingly, the study was carried out under the following experimental conditions.

Denopamine, suspended in 0.25% CMC aqueous solution, was given orally to rats at a dose of 10, 20 or 40 mg/kg for 14 days once daily (8:00 A.M.) in a volume of 0.5 ml/100 g body weight. The control group was given an equivalent volume of 0.25% CMC solution alone. Administration of denopamine in the diet (Nihon Clea, CE-2 powder) was also carried out in order to maintain effects of denopamine to a constant level for long term as compared with compulsory p.o. treatment, because it has been reported that the daily food intake of rats occurs not only during the dark phase but also during the light phase (12, 13). Denopamine was given to rats so that their intake was 20 or 40 mg/kg/day for 14 days. The diet including denopamine was freshened at 8:00 A.M. each day.

The inotropic response to denopamine was assessed between 48 and 56 hr after the last dosing, because the positive inotropic effect of denopamine at a high dose remained even after 24 hr.

**Repeated treatment with isoproterenol:** As death was observed at a dose of 100 μg/kg, s.c., or at a dose of more than 100 μg/kg, t.i.d., for 3 days, doses of isoproterenol for repeated treatment were selected so as to be safe but sufficiently effective (see results): 5 and 50 μg/kg, s.c.

Isoproterenol in 0.9% NaCl solution was administered by s.c. injection to rats thrice daily (8:00 A.M., 12:30 P.M. and 17:00 P.M.) in doses of 5 and 50 μg/kg for 3 days. The control group was administered with 0.9% NaCl solution alone.

The inotropic response to isoproterenol was assessed between 16 and 24 hr after the last injection.

**Inotropic effects in drug-treated rats:** Drug-treated rats were anesthetized with pentobarbital sodium (50 mg/kg, i.p.), and LV dp/dt, heart rate and blood pressure was measured, according to the method described above. Drugs were administered via the cannulated femoral vein with increasing doses by a factor of three at 3 min intervals. Denopamine was dissolved in the corresponding amount of HCl and 0.9% NaCl solution.

**After the completion of the measurements,** the weight of the whole heart was measured.

**3H-Dihydroalprenolol (3H-DHA) binding assay:** Isolated membranes were prepared according to U’Prichard et al. (14) with some modifications. Briefly, isolated ventricles were minced and homogenized using a Polytron (setting 6, 30 sec) in 20 volumes of
ice-cold 50 mM Tris-HCl buffer (pH 7.5, 25°C) and centrifuged at 28,000×g for 10 min. The pellet was rehomogenized and centrifuged as before. The resultant pellet was finally suspended to the concentration of 7 mg original wet tissue per 1 ml buffer. The aliquot (1 ml, about 300 to 600 μg of protein) of the particulate suspension was incubated with 3H-DHA (50 μl, 0.1–7 nM) at 25°C with and without 10 μM (±)-propranolol. After 30 min, the reaction was stopped by adding 8 ml of ice-cold 50 mM Tris-HCl buffer, and the incubated medium was filtered under reduced pressure through glass fiber filters (Whatman GF/C). The filters were washed with an additional 8 ml of ice-cold buffer. The radioactivity of bound 3H-DHA on the filter was measured by a liquid scintillation spectrometer (Packard, 460 CD). Non-specific binding of 3H-DHA was assessed in the presence of 10 μM (±)-propranolol. Specific binding was defined as the difference between total and non-specific binding.

Drugs: Drugs were obtained from the following sources: denopamine (Tanabe Seiyaku), (±)-isoproterenol hydrochloride (Kaken Kagaku), 3H-dihydroalprenolol (88 Ci/mmol, Amersham) and (±)-propranolol hydrochloride (Nakarai Chemicals).

Statistical analysis: The results were expressed as means±S.E. The dose causing a 50% increase in LV dp/dt max of the control (denoted as ED50) was obtained by the inverse estimate of regression with confidence limits for 95% probability. In the comparison of cardiac weight, the data were analyzed using the one-way analysis of variance. Other statistical analysis, as represented in the figure and tables, were carried out using one-way analysis of variance, the Kuraskal-Wallis test, the paired t-test and Student’s t-test. Results were considered significant if P values were >0.05.

Results

Cardiovascular effects of the dosage used for chronic or repeated treatment: The effects of single intra-gastric administration of denopamine on LV dp/dt max, heart rate (HR) and mean blood pressure (MBP) in anesthetized rats are shown in Fig. 1. Denopamine at a dose of 0.1 mg/kg, i.g., caused an increase in LV dp/dt max without significantly altering heart rate and blood pressure. The ED50 was 0.77 (0.52–1.07) mg/kg, i.g. Denopamine at a dose of 10 mg/kg, i.g., produced maximal responses of LV dp/dt max (a 150% increase) and heart rate (a 27% increase) and an insignificant decrease in mean blood pressure.

Time course of cardiovascular effects of denopamine (10, 20 and 40 mg/kg) after p.o. administration is shown in Fig. 2. Duration of positive inotropy of denopamine was more than 8 hr at doses of 10 and 20 mg/kg, and it was more than 24 hr at a dose of 40 mg/kg. A significant increase in heart rate was recognized until 8 hr at doses of 20 and 40 mg/kg. Mean blood pressure was not changed by denopamine.

Figure 3 shows the effects of single s.c. administration of isoproterenol. Isoproterenol produced significant increases in LV dp/dt max and heart rate at a dose of 0.03 μg/kg or more,
Fig. 2. Time course of cardiovascular effects of denopamine by single p.o. administration. Measurements were carried out in the anesthetized state. ○, control; ●, 10 mg/kg, p.o.; △, 20 mg/kg, p.o.; ▲, 40 mg/kg, p.o. Each point represents the mean of four to nine experiments with S.E. Some of the standard errors are within the symbols. Significance, *P<0.05, **P<0.01 vs. the control (analysis of variance).

Fig. 3. Effects of single s.c. administration of isoproterenol on LV dp/dt max, heart rate (HR) and mean blood pressure (MBP) in anesthetized rats. Each point represents the mean of five experiments with S.E. in terms of the peak effect observed in 2 to 30 min after administration. Some of the standard errors are within the symbols. Control values (mean±S.E.) are as follows: LV dp/dt max, 8200 ±180 mmHg/sec; heart rate, 370±10 beats/min; mean blood pressure, 102±5 mmHg. Significance, ***P<0.01 vs. predosing value (paired t-test).

s.c., and it produced a significant decrease in mean blood pressure at a dose of 1 μg/kg or more, s.c. Isoproterenol at a dose of 5 μg/kg, s.c., produced a 107% increase in LV dp/dt max, and this was associated with a 30% increase in heart rate and a 34% decrease in mean blood pressure (by the analysis of regression of data in Fig. 3). As evidenced from the figure, 50 μg/kg of isoproterenol, s.c., was a sufficient dose to induce maximum effects on LV dp/dt max and heart rate.

Influence of chronic administration of denopamine: The cardiovascular effects of denopamine in anesthetized rats, which had been given denopamine for 14 days, are shown in Fig. 4. As shown in 4A, the basal levels of LV dp/dt max, heart rate and mean blood pressure in the treated groups were not significantly different from those of the control group. In the 10 and 20 mg/kg denopamine groups, the positive inotropic and chronotropic effects were not affected by chronic administration. In the 40 mg/kg group, however, the positive inotropic effect of denopamine (i.v.) was attenuated slightly but significantly at lower doses; and at higher doses, it was similar to that in the control group. As shown in Table 1, the ED50 was significantly greater than that for the control group, and the dose ratio was increased to 1.8. In the 40 mg/kg group, the positive chronotropic effect of denopamine (i.v.) tended to decrease at lower doses. Figure 4B shows relationship between increases in LV dp/dt max and heart rate induced by denopamine, indicating that this relationship was not affected by chronic treatment with this drug. The effect of denopamine (i.v.) on mean blood pressure was not affected by chronic treatment.

When denopamine was administered to rats in the diet at a dose of 20 or 40 mg/kg/day
Fig. 4. Cardiovascular effects of denopamine in rats chronically treated with denopamine. A. Effects of i.v. increasing doses of denopamine on LV dp/dt\textsubscript{max}, heart rate (HR) and mean blood pressure (MBP) in anesthetized rats. B. Relationship between increases in LV dp/dt\textsubscript{max} and heart rate induced by denopamine. Rats were treated with denopamine once daily for 14 days. Each point shows the mean value of eight experiments with S.E. Control animals (○) and animals treated with denopamine at 10 (●), 20 (△) and 40 mg/kg (▲), respectively. Some of the standard errors are within the symbols. Significance, **P<0.01 vs. the control group (analysis of variance).

Table 1. The dose of denopamine and isoproterenol to increase LV dp/dt\textsubscript{max} by 50% (ED50) in drug-treated rats

| Drugs                  | n  | ED50 (μg/kg, i.v.)         | Dose ratio |
|------------------------|----|---------------------------|------------|
| Denopamine (14 days)   |    |                           |            |
| control                | 8  | 1.74 (1.36–2.24)          | 1.0        |
| 10 mg/kg, p.o.         | 8  | 1.72 (1.49–1.99)          | 1.0        |
| 20 mg/kg, p.o.         | 8  | 1.99 (1.68–2.36)          | 1.1        |
| 40 mg/kg, p.o.         | 8  | 3.15 (2.77–3.59)*         | 1.8        |
| control                | 8  | 1.25 (0.76–2.06)          | 1.0        |
| 20 mg/kg/day in diet   | 8  | 1.08 (0.63–1.85)          | 0.9        |
| 40 mg/kg/day in diet   | 8  | 1.35 (0.82–2.22)          | 1.1        |
| Isoproterenol (3 days) |    |                           |            |
| control                | 7  | 0.018 (0.014–0.023)       | 1.0        |
| 5 μg/kg, s.c., t.i.d.  | 8  | 0.043 (0.025–0.075)*      | 2.4        |
| 50 μg/kg, s.c., t.i.d. | 8  | 0.123 (0.026–0.573)**     | 6.8        |

ED50 represents the dose causing a 50% increase in LV dp/dt\textsubscript{max}. Dose ratio was calculated as (ED50 in the treated group)/(ED50 in the control group). Values in parentheses are 95% confidence limits. *P<0.05, **P<0.01, compared with the control group (Kruskal-Wallis test).
for 14 days, the ED50 of denopamine for positive inotropy was not influenced by chronic treatment (Table 1). The effects of denopamine (i.v.) on heart rate and mean blood pressure were also not affected by chronic treatment (data not shown).

**Influence of repeated treatment with isoproterenol:** Figure 5A and Table 1 show the cardiovascular effects of isoproterenol (i.v.) and ED50 in anesthetized rats after repeated treatment with isoproterenol. In the 5 \( \mu g/kg \) group, the positive inotropic effect of isoproterenol (i.v.) was attenuated slightly but significantly at lower doses with a 2.4-fold increase of the ED50 (Table 1). In the 50 \( \mu g/kg \) group, the dose-response curve of isoproterenol on LV dp/dt \(_{max} \) was shifted to the right by 6.8-fold at the ED50 and the maximal response was depressed to approximately 70% of that obtained in the control. The positive chronotropic effect of isoproterenol (i.v.), however, only tended to decrease in the treated groups. Figure 5B shows the relationship between LV dp/dt\(_{max} \) and heart rate induced by isoproterenol. In the 50 \( \mu g/kg \) group, the responsiveness of LV dp/dt \(_{max} \) was more depressed than that of heart rate. The effect of isoproterenol (i.v.) on mean blood pressure was not affected in the treated groups.

**Cross tolerance:** The inotropic response to denopamine in the isoproterenol (50 \( \mu g/kg \), thrice daily for 3 days)-treated preparation was examined (Fig. 6A). The positive inotropic effect of denopamine (i.v.) was attenuated slightly but significantly at lower doses, but the attenuation was less than that with isoproterenol (i.v.) (cf. Fig. 5A). Moreover, the maximal response to denopamine was not less than that in the control group. Accordingly, denopamine, unlike isoproterenol, showed no influence on the relationship between increases in LV dp/dt \(_{max} \) and heart rate induced by denopamine.

**Fig. 5.** Cardiovascular effects of isoproterenol in rats treated with isoproterenol. A. Effects of i.v. increasing doses of isoproterenol on LV dp/dt \(_{max} \), heart rate (HR) and mean blood pressure (MBP) in anesthetized rats. B. Relationship between increases in LV dp/dt \(_{max} \) and heart rate induced by isoproterenol. Rats were treated with isoproterenol thrice daily for 3 days. ○, control group (n=7); △, 5 \( \mu g/kg \) group (n=7); □, 50 \( \mu g/kg \) group (n=8). Some of the standard errors are within the symbols. Significance, *P<0.05, **P<0.01 vs. the control group (analysis of variance).
in the 50 μg/kg isoproterenol treated rats.

Conversely, the influence of chronic treatment with denopamine on the inotropic effect of isoproterenol (i.v.) was examined (Fig. 6B). The positive inotropic effect of isoproterenol (i.v.) in the denopamine (40 mg/kg, p.o.)-treated group was attenuated slightly only at lower doses. The extent of attenuation was similar to that in the case with denopamine (i.v.) (cf. Fig. 4A).

Changes in cardiac weight by chronic treatment with drugs: The weight of the whole heart in the 40 mg/kg denopamine (p.o.) group slightly increased by 7.4% (P<0.01) of that in the control group, and those in the other denopamine-treated groups were not changed. The cardiac weight in the 50 μg/kg isoproterenol group increased by 27.1% (P<0.01), while that in the 5 μg/kg isoproterenol group was not altered.

Influences of denopamine and isoproterenol treatment on specific 3H-DHA binding: Table 2 shows the binding parameters for specific 3H-DHA binding to the cardiac membranes obtained from the rats treated with denopamine or isoproterenol. Repeated treatment with isoproterenol (5 and 50 μg/kg) significantly decreased the maximum number of binding sites (B_{max}) by approximately 15% without alteration in either the dissociation constant (K_d) or the Hill coefficient. Chronic treatment with denopamine (20 and 40 mg/kg/day) in the diet caused no changes in any of the parameters and neither did chronic treatment with 10 and 20 mg/kg denopamine, p.o. Chronic treatment with 40 mg/kg denopamine, p.o., decreased B_{max} (about 25%)
Table 2. The specific binding parameters for \( ^3 \text{H}-\text{DHA} \) to the cardiac membrane fractions obtained from the rats treated with denopamine or isoproterenol

| Drugs                  | n  | \( B_{\text{max}} \) (fmol/mg protein) | \( K_d \) (nM) | Hill coefficient |
|------------------------|----|----------------------------------------|-----------------|------------------|
| Denopamine (14 days)   |    |                                        |                 |                  |
| control                | 4  | 54.2±3.6                               | 0.42±0.02       | 1.16±0.17        |
| 10 mg/kg, p.o.         | 4  | 51.3±4.6                               | 0.52±0.09       | 1.22±0.10        |
| 20 mg/kg, p.o.         | 4  | 48.7±4.5                               | 0.49±0.04       | 1.05±0.09        |
| 40 mg/kg, p.o.         | 4  | 39.6±2.4*                              | 0.39±0.03       | 1.12±0.15        |
| control                | 6  | 53.7±3.5                               | 0.67±0.04       | 0.97±0.04        |
| 20 mg/kg/day in diet   | 6  | 56.4±2.2                               | 0.63±0.07       | 1.03±0.02        |
| 40 mg/kg/day in diet   | 6  | 59.5±3.5                               | 0.67±0.06       | 1.01±0.03        |
| Isoproterenol (3 days) |    |                                        |                 |                  |
| control                | 6  | 48.1±1.3                               | 0.50±0.02       | 1.06±0.04        |
| 5 \( \mu \)g/kg, s.c., t.i.d. | 6  | 41.1±1.7**                             | 0.48±0.03       | 1.07±0.09        |
| 50 \( \mu \)g/kg, s.c., t.i.d. | 6  | 40.6±1.3**                             | 0.53±0.06       | 1.01±0.01        |

Each value represents the mean±S.E. of 4 or 6 experiments, and each was performed in duplicate determinations. Significance *\( P<0.05 \), **\( P<0.01 \) vs. the control group (Student's t-test).

significantly without alteration in the \( K_d \) and Hill coefficient.

Discussion

In the present study, left ventricular pressure and rate of its change (LV dp/dt) in rat hearts were recorded without thoracotomy and major operation, and the basal level of LV dp/dt \( \text{max} \) in each group was found to be almost identical. The present study revealed that denopamine showed positive inotropy by oral administration and that the positive inotropic effect of denopamine was more pronounced than the positive chronotropic effect, as had been shown in various species of animals (1). Moreover, its positive inotropic effect was extremely long lasting at high doses (Fig. 2).

The decrease in the number of \( \beta \)-adrenoceptor and uncoupling of the \( \beta \)-adrenoceptor-adenylate cyclase complex have been proposed as the mechanism for desensitization induced by \( \beta \)-adrenoceptor agonists (15, 16). In the present study, repeated treatment with isoproterenol for 3 days of rats produced an attenuation of the effect of isoproterenol on LV dp/dt \( \text{max} \) and a decrease in \( B_{\text{max}} \). The dose-response curve to isoproterenol for LV dp/dt \( \text{max} \) in the 5 \( \mu \)g/kg group was shifted to the right only at lower doses, but the 50 \( \mu \)g/kg group exhibited both the rightward shift of the dose-response curve and the decrease in the maximal response. This suggests that the rightward shift of the dose-response curve in the isoproterenol-treated groups is caused by down-regulation. However, the decrease in the maximal response in the 50 \( \mu \)g/kg group might be induced by additional mechanisms, for example, a kind of uncoupling of the \( \beta \)-adrenoceptor-adenylate cyclase complex, because the extent of down-regulation was not so marked.

Chronic administration of denopamine at doses of 10 and 20 mg/kg, p.o., for 14 days did not produce desensitization of positive inotropy and down-regulation. However, the 40 mg/kg group exhibited a rightward shift of the dose-response curve for positive inotropy at lower doses without a decrease in the maximal response. This means that increasing the dose of denopamine can overcome the diminished response, in contrast to the high dose of isoproterenol. The 40 mg/kg group also showed a decrease in \( B_{\text{max}} \) and thus down-regulation appears to explain desensitization of positive inotropy to denopamine. Incidentally, the dose of
40 mg/kg was extremely higher than the effective dose; the ED50 was 0.77 mg/kg. On the other hand, chronic treatment with denopamine (20 and 40 mg/kg/day) in the diet for 14 days did not produce desensitization and down-regulation. These results suggest that with denopamine, desensitization scarcely occurs in positive inotropy in rats at the effective doses.

Isoproterenol of 5 ,ug/kg, s.c., which caused a 100% increase in LV dp/dt max, produced desensitization of positive inotropy. However, denopamine of 10 mg/kg, p.o., which caused about 150% increase in LV dp/dt max produced no desensitization. Although the route of administration of denopamine differs from that of isoproterenol, this indicates that isoproterenol produces desensitization more easily than denopamine in relation to their positive inotropic activity.

It has been shown that agonist-promoted desensitization is mediated by phosphorylation of , adrenoceptors via cyclic AMP (17, 18), and the ability to induce desensitization correlates with the intrinsic activity of drugs to induce cyclic AMP accumulation (19). The degree of elevation in cardiac cyclic AMP with denopamine is smaller than that with isoproterenol in the presence of equipotent cardiotonic effects (20), and low sarcolemmal adenylate cyclase activation with denopamine (21) has also been demonstrated. Moreover, a partial agonistic property of denopamine in the binding study of , adrenoceptor has been shown (22, 23). Thus, the partial agonistic property of denopamine may explain, at least partly, its weak desensitization through weak phosphorylation of , adrenoceptor.

It has been demonstrated that repeated treatment with isoproterenol in the pithed rat results in desensitization of its positive chronotropy as well as positive inotropy (9). In the present study, repeated treatment with denopamine and isoproterenol induced a tendency for desensitization of positive chronotropy. However, it is of interest to note that no desensitization on blood pressure was observed.

It has been reported that isoproterenol-induced down-regulation of , adrenoceptor results in a complete suppression of the inotropic response to prenalterol and pirbuterol (7). However, denopamine produced a positive inotropic effect even in the preparation desensitized by isoproterenol (50 ,ug/kg), although the effect of denopamine was slightly attenuated at lower doses (Fig. 6A). This result, as well as the data presented in Figs. 1 and 4, suggests that the intrinsic activity of denopamine for positive inotropy is higher than that of prenalterol and pirbuterol. On the other hand, the response to isoproterenol in the preparation desensitized by denopamine (40 mg/kg) was also attenuated, and the extent of the attenuation was similar to that with denopamine (Fig. 6B). Thus, denopamine could produce cross tolerance to isoproterenol, but to a lesser extent than prenalterol and pirbuterol. However, it is noteworthy that the different response between isoproterenol and denopamine was found in the preparation desensitized by isoproterenol, suggesting that the mechanism for the inotropic action of dopamine is different from that of isoproterenol.

It has been demonstrated that repeated treatment with isoproterenol produces cardiomegaly (24, 25). In the present study, the cardiac weight increased in each maximum dose-treated group of denopamine and isoproterenol. The degree of the increase in cardiac weight in the denopamine-treated group was weaker than that in the isoproterenol-treated group. This is comparable to the order of the degree of cardiac desensitization. The increase in cardiac weight may also be involved in cardiac desensitization (6).

In conclusion, as denopamine produced desensitization only in a very high dose which caused an increase in cardiac weight, it is suggested that chronic administration of denopamine hardly results in desensitization of its positive inotropy at the effective doses.

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