Myocarditis Induced by Sympathomimetic Amines (I)

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Production of myocardial lesions with sympathomimetic amines was studied in rats. Subcutaneous administration of isoproterenol at the daily doses of 1.2 mg and 0.7 mg per kg for 14 days caused a marked diffuse myocarditis. The myocardial lesions were detected by electrocardiogram 1 week after the beginning of the administration. Norepinephrine, nor-fenefrine and phenylephrine did not show any pathologic change in the myocardium. The significance of the toxic effects of these amines was studied.

MANY types of sympathomimetic amines are widely used in therapeutics because of their potent cardiovascular and bronchodilator actions. On the other hand, some of these compounds show injurious effect on the cardiovascular system itself. In 1909, FLEISHER et al¹ described experimental myocarditis caused by epinephrine. Since then, there have been many reports of cardiac lesions induced by epinephrine,²⁻⁴ norepinephrine,⁵⁻⁸ and several other sympathomimetic amines.^{6,9} Previously, the authors found slight lymphocytic cell clumps in the myocardium of rats treated with norfenefrine as well as rats which were untreated.¹⁰ The present study was devised to examine myocarditis resulting from the toxicity of representative sympathomimetic amines including norfenefrine.

MATERIALS AND METHODS

Sprague-Dawley male rats of 9 weeks weighing 280–320 g were used. The drugs tested were norepinephrine, isoproterenol, norfenefrine and phenylephrine. Preliminary studies were carried out to establish the effects of these drugs on the blood pressure and heart rate using 25 rats. After carotid artery cannulation under intraperitoneal urethan anesthesia, blood pressure and electrocardiogram were recorded at frequent intervals by “polygraph” – multichannel ink writing oscil-

lograph (San-ei instrument Co., Ltd.).

Forty five rats were divided into 9 groups and each group received subcutaneous administration of the drugs at 24 hour intervals for 13 days in accordance with the injection schedule described below.

Group I	control; 1 ml/kg of physiological salt solution
Group II	norepinephrine 1.0 mg/kg
Group III	norepinephrine 0.6 mg/kg
Group IV	isoproterenol 1.2 mg/kg
Group V	isoproterenol 0.7 mg/kg
Group VI	norfenefrine 9.0 mg/kg
Group VII	norfenefrine 5.8 mg/kg
Group VIII	phenylephrine 9.7 mg/kg
Group IX	phenylephrine 6.2 mg/kg

Electrocardiograms were recorded before administration of the drugs and 7 days after commencement of administration under intraperitoneal pentobarbital anesthesia by limb leads. Histologic examination was done after sacrificing the animals on the 14th day of the experiment approximately 24 hours after the last injection.

RESULTS

Blood pressure: The effects of the amines on the mean blood pressure are showed in Fig. 1. Norepinephrine distinctly elevated the blood pressure between 20–30 mmHg (mean: 23 mm-

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Fig. 1. Blood pressure and heart rate of the rats treated with sympathomimetic amines

Fig. 2. Electrocardiograms of a rat treated with isoproterenol 1.2 mg/kg.

Hg) for approximately 10 minutes after administration. Isoproterenol constantly depressed the blood pressure between 20–50 mmHg (mean: 42.3 mmHg) for two or three hours. Norfenefrine and phenylephrine showed a slight pressor activity ranging between 7–25 mmHg (mean: 10 mmHg) and 7–27 mmHg (mean: 15 mmHg), respectively. The dose and response relationship was not definitive for each amine at the doses used in this experiment.

Heart rate: Significant changes in the heart rate were induced by 1.2 mg and 0.7 mg per kg of isoproterenol. The heart rate was raised by 30–40 beats per minute in each case. No marked change was observed with norepinephrine, norfenefrine and phenylephrine (Fig. 1).

Electrocardiogram: The same electrocardiogram recordings were obtained through the careful fixation of the animals so as to avoid any change in the electrical axis. One of the characteristic findings of the electrocardiogram of rats was the elevation of the ST and the T which began from the mid-portion of the QRS segment. In Fig. 2 such findings in a normal rat are shown. Norepinephrine, norfenefrine and phenylephrine did not produce any remarkable change except for occasional tachycardia. In isoproterenol treated rats, significant depression of the ST segment to 0.1 mV and the Q wave to 0.06 mV was frequently observed, as well as the inverted T in leads I and II. These findings were considered to be signs of widespread myocardial lesion. All ani-

TABLE I ELECTROCARDIOGRAM FINDINGS

Drug and Dose	PR (msec)	QRS (msec)	QT (msec)	ST-T depression	inverted T	deep Q
Control	36.7-46.7	16.7-22.0	52.0-70.0	0/5	0/5	0/5
Norepinephrine						
1.0 mg/kg	41.6-43.4	16.7-20.0	55.0-66.7	0/5	0/5	0/5
0.6 mg/kg	40.0-45.0	16.7-18.3	60.0-66.7	0/5	0/5	0/5
Isoproterenol						
1.2 mg/kg	40.0-46.7	16.7-18.3	58.3-91.6	5/5	5/5	4/5
0.7 mg/kg	41.6-50.0	18.3-20.0	50.0-78.3	4/5	5/5	5/5
Norfenefrine						
9.0 mg/kg	41.6-45.0	16.7-20.0	58.3-76.0	0/5	0/5	0/5
5.8 mg/kg	40.0-45.0	16.7-18.5	58.3-76.0	0/5	0/5	0/5
Phenylephrine						
9.7 mg/kg	41.7-50.0	16.7-18.3	51.6-75.0	0/4	0/4	0/4
6.2 mg/kg	40.0-45.0	16.7-18.3	61.6-75.0	0/5	0/5	0/5

TABLE II PATHOLOGIC FINDINGS

Drug and Dose	Heart weight/100 g Body weight	Histologic findings
Control	0.36 ± 0.05	n.p. (minute lymphocytic infiltrate; 2/5)
Norepinephrine		
1.0 mg/kg	0.38 ± 0.03	n.p. (minute lymphocytic infiltrate; 2/5)
0.6 mg/kg	0.37 ± 0.04	n.p.
Isoproterenol		
1.2 mg/kg	0.47 ± 0.05*	marked myocarditis; 5/5
0.7 mg/kg	0.44 ± 0.02*	marked myocarditis; 5/5
Norfenefrine		
9.0 mg/kg	0.39 ± 0.07	n.p.
5.8 mg/kg	0.35 ± 0.01	n.p. (minute lymphocytic infiltrate; 2/5)
Phenylephrine		
9.7 mg/kg	0.39 ± 0.05	n.p. (minute lymphocytic infiltrate; 1/4)
6.2 mg/kg	0.40 ± 0.02	n.p. (minute lymphocytic infiltrate; 2/5)

* Statistically significantly difference from control ($p < 0.05$) n.p. : not particular

mals of group IV and V showed such signs of myocardial lesions on the electrocardiogram. Results of an analytical study of the electrocardiograms are shown in Table I.

Pathologic change: Marked response of the heart to isoproterenol was noticed. The heart was enlarged in all animals of groups IV and V. Heart weight was 0.47 ± 0.05 g per 100 g body weight in group IV and 0.44 ± 0.02 g per 100 g body weight in group V, in contrast to 0.36 ± 0.05 g per 100 g body weight in the control group. In other groups treated with norepinephrine, norfenefrine and phenylephrine no cardiac enlargement was observed (Table II).

Microscopically, the myocardium of the iso-

proterenol treated groups showed remarkable diffuse or focal myocarditis (Fig. 3). A large and patchy foci of myocarditis showing organization with fibroblastic proliferation and lymphocytic infiltrate were observed. No distinct polymorph-nuclear leucocytic infiltration, hemorrhage or infarct-like lesions was present. In general, these myocardial lesions were concentrated in the sub-endocardial region of the left ventricle and near the apex. In case of severe lesion, the right ventricle near the apex was sometimes involved. The coronary artery and its branches were intact. All of the ten cases in groups IV and V treated with isoproterenol at the doses of 1.2 mg and 0.7 mg per kg, respectively, showed the severe myocardi-

tis described above.

Animals treated with norepinephrine, norfenefrine and phenylephrine were free from myocardial lesions. No involvement of muscle fibers was revealed by photomicroscopic observations in the groups treated with these amines. However, very small clumps of lymphocytes in interstitial spaces were noticed in many groups, including the control group. There was no significant difference in the frequency of such lymphocytic clumps between the control and other groups. The results

of the pathologic findings are summarized in Table II. No specific findings were detected in the lung, liver, kidney, adrenal, spleen, pancreas, stomach, intestine, colon, bone marrow, thymus and brain.

DISCUSSION

From the present study, it is evident that isoproterenol possesses a distinct property to produce myocardial lesions in rats at the doses of our experiment, while norepinephrine, norfene-

Fig. 3. Photomicrographs of a heart treated with isoproterenol 1.2mg/kg. Note the marked proliferation of perimysial cells and fibroblasts with lymphocytic infiltration. a. $\times 40$ b. $\times 100$

frine and phenylephrine have less active cardiotoxicity.

The production of cardiac lesions with isoproterenol was first reported by RONA and CHAPPEL (1959).^{11,12} In their reports, isoproterenol injection was considered to be a reliable method for producing experimental myocardial infarct-like lesions. Among the many types of sympathomimetic compounds, isoproterenol is known to be one of the most potent cardiotoxic amines.^{9,11,12} It is reported that myocardial necrosis can be produced by a dose of 0.118 μ moles (0.02 mg) per kg.⁹ Recently, KIMURA et al.¹³ proposed a diagnostic method for detecting latent coronary insufficiency through the infusion of isoproterenol. When coronary insufficiency is present, the occurrence of angina-like precordial pain and ST depression are frequently present. They reported that they used 70–100 μ g intramuscularly or 8–60 μ g by intravenous infusion of isoproterenol for this purpose. There are other reports on the side effects of isoproterenol in clinical therapeutics. Tachycardia and precordial discomfort have reportedly been occasionally observed.^{14–17} Although the toxic dose has been established pharmacologically, it is still not known whether this dose is the same for cases with pathological heart conditions. The authors feel that greater care should be paid in the administration of isoproterenol.

There have been different opinions about the mechanism of the action of such sympathomimetic amines on the myocardium. One is that the lesions are a direct effect of isoproterenol on the myocardial cells as WARTMAN¹⁸ has postulated. Some hold that these injuries are caused by the cardiovascular actions of the amine such as depressed blood pressure, increased heart rate, increased contractile force and left ventricle work, etc.^{9,11} There are other investigators who consider that the metabolic effects of the amine are also important.^{9,19}

In our experiment, the character of the cardiac lesions closely resembles myocarditis rather than myocardial infarction. Marked proliferation of perimysial cells and fibroblasts, abundant lymphocytic infiltrate and absence of neutrophils are noticed, whereas fresh infarct-like changes or foci of degenerative muscle bundles were not present. From these findings it is debatable whether the primary cellular response to isoproterenol is the direct degeneration of myocardial cells or an interstitial inflammatory response without cardiac necrosis. There are several reports in which the

cardiac lesions have been described as necrosis of the myocardium. At present the authors postulate that smaller dosages cause minimal degenerative changes in the myocardium and evident consecutive response in interstitial cells, while larger doses tend to induce massive myocardiocytolysis.

Cardiac lesions with other sympathomimetic amines have been known experimentally^{6,8,9} as well as clinically.²⁰ Cardiac impairment with epinephrine has been established since JOSUÉ (1904)²¹ in experiments. ROSENBLUM,⁹ who investigated the cardiotoxicity of 15 sympathomimetic amines, reported isoproterenol and phenylephrine to show injurious effects from doses of 0.118 μ moles (0.02 mg) per kg, norepinephrine from 1.18 μ moles (0.20 mg) per kg and epinephrine, nordefrin and methoxamine from 11.8 μ moles (2.16 mg, 2.59 mg and 2.91 mg, respectively) per kg. In therapeutics, SZAKACS and CANNON¹⁹ described "norepinephrine myocarditis" in man following prolonged infusion of this amine. In our experiment no remarkable change was found with norepinephrine, norfenefrine and phenylephrine. We consider that these differences can be explained on the basis of doses, strain of animals and other conditions. Slight patchy lymphocytic infiltrates in the control group and some of the other groups treated with norepinephrine, norfenefrine and phenylephrine must be considered incidental findings which is occasionally found in experimental animals.¹⁰

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