Myocardial Hypertrophy Resulting from Low Dosage Isoproterenol Administration in Rats[1] (35243)

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In several recent studies, isoproterenol has been shown to induce myocardial hypertrophy in rats at doses substantially below the levels which produce myocardial lesions. Doses of 5 mg/kg administered twice daily for 2 days produce both increased heart weight and microscopically detectable myocardial lesions; whereas smaller doses, 0.08 and 1.25 mg/kg administered in the same way, produce only hypertrophy without myocardial lesions (1). Cellular metabolic effects of isoproterenol have been documented in dogs at a dose of 0.036 mg/kg/day administered by continuous infusion for 6 days (2).

The following study was undertaken to determine whether an even lower dose of isoproterenol would induce myocardial weight gain and to determine whether or not this weight gain could be associated with measurable hemodynamic changes.

Methods. Male Sprague-Dawley rats weighing 180 to 220 g were housed four to a cage and fed a standard laboratory diet and tap water *ad libitum.* Isoproterenol was administered subcutaneously, once daily, in a dose of 0.02 mg/kg. Saline in equivalent volumes was given daily to control groups of rats. Groups of rats were injected for either 13 or 31 days.

The heart rate in four rats from each group was measured for 1 hr preceding and 5 hr following drug or saline administration. Light ether anesthesia was used, and the heart rate was determined from needle electrocardiograms.

At the conclusion of the experiment (13 or 31 days), each rat was fasted 24 hr and killed by a blow on the head. The heart and both kidneys were removed. The capsule and peripelvic fat were stripped from the kidneys. The atria were excised from the hearts, and ventricles were opened, clots were removed, and then blotted dry. The weight of the kidneys and heart were determined on a balance accurate to 1 mg. The combined right and left ventricle was dried for 48 hr under a vacuum at 180° and reweighed.

Results. Figure 1 illustrates the mean diff-

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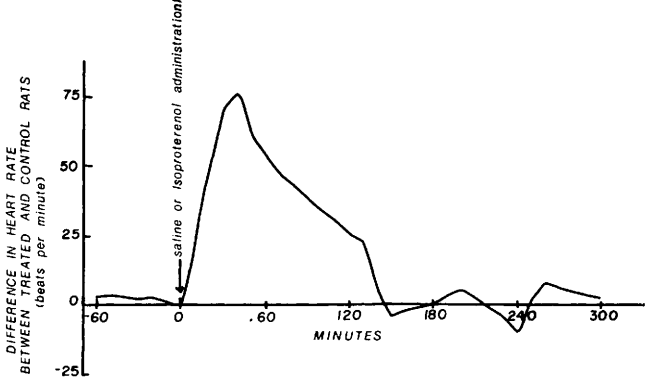

FIG. 1. The mean difference in heart rates of four rats in response to saline and four rats in response to isoproterenol (0.02 mg/kg) is illustrated.

TABLE I.[a]

	13 days		31 days	
	(1) Control	(2) Isoproterenol	(3) Control	(4) Isoproterenol
No.	12	8	9	7
Body wt (g)	324	328	385	404
Wet heart wt (mg)	963 ± 26	1073 ± 31	1077 ± 40	1270 ± 67
% Dry wt	22.6 ± 0.2	22.6 ± 0.3	21.7 ± 0.3	23.2 ± 0.6
Dry heart wt (mg)	217 ± 6	247 ± 3	234 ± 8	294 ± 15
p [Col. (1)(2); (3)(4)]		<0.01		<0.01
Dry heart wt / Wet kidney wt	0.075 ± 0.003	0.085 ± 0.001	0.078 ± 0.002	0.093 ± 0.003
p [Col. (1)(2); (3)(4)]		<0.05		<0.01
p [Col. (1)(3)]			NS	

[a] Column (1), saline treated animals for 13 days; Column (2), isoproterenol treated animals once daily for 13 days; Column (3), saline treated animals for 31 days; and Column (4), isoproterenol treated animals once daily for 31 days. Data are expressed as means ± SEM; p value determined by unpaired t test assuming differing variances between groups.

erences in heart rate response of four rats in each group to saline or isoproterenol injection. Tachycardia was noted in the group receiving isoproterenol. One of nine rats treated with isoproterenol for 13 days and two of nine rats treated for 31 days died before the end of the experiment.

Table I lists for each group of rats the mean body weight, wet heart weight, dry heart weight, and percentage dry heart weight. The standard error of the mean is given for each value. In order to compare groups of rats differing ages (13 day and 31 day rats) the ratio of dry heart weight to kidney weight was calculated. This ratio was found to remain constant despite changes in body weight. The probability values from an unpaired t test, assuming differing variances between groups of rats, are given for dry heart weight and the ratio of dry heart weight to kidney weight. The group receiving isoproterenol showed significant wet and dry heart weight gain over control groups. The rats treated with isoproterenol for 13 days showed a 14% dry heart weight gain over controls, and the 31 day rats showed a 26% gain over controls (Fig. 2).

Discussion. Myocardial hypertrophy has been produced in animals by a wide variety of methods including coarctation, anemia, exercise, thyroid hormone, and renal hypertension (3). Isoproterenol in high doses has been shown to produce cardiac weight gain. However, this has in general been attributed to the toxic effects of the drug. The weight gain has usually been associated with myocardial lesions and a decrease in the percentage dry heart weight suggesting edema formation. In this experiment, heart weight gain was noted at much lower isoproterenol doses than those reported to be associated with pathologic lesions. No decrease in

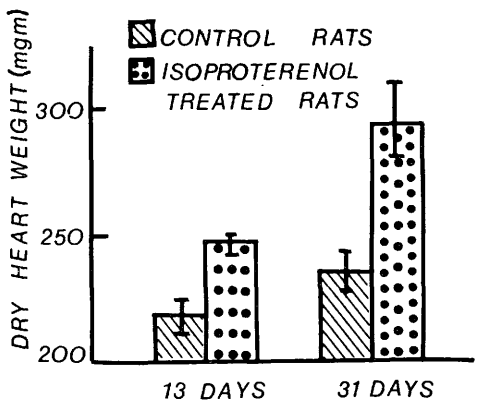

FIG. 2. Dry heart weight of rats given saline for 13 and 31 days as compared to rats given isoproterenol (0.02 mg/kg/once daily) for 13 and 31 days.

the percentage dry heart weight was noted, suggesting that cardiac edema was not induced.

These results indicate that significant heart weight gain, *i.e.*, myocardial hypertrophy, takes place when essentially therapeutic doses of isoproterenol are given over long periods. Norman (3) and Badeer (4) have pointed out that all stimuli which cause cardiac hypertrophy have in common the need for increased cardiac work, increased oxygen consumption, and increased tension-time relationship. This study would support the view that isoproterenol is such a stimulus, since chronotropic effects were demonstrated in the treated animals. Isoproterenol may therefore, by causing transient chronotropic and inotropic effects, stimulate a more sustained anabolic response at the cellular level which leads, in time, to cardiac hypertrophy.

Summary. Isoproterenol, in lower doses than previously reported, was administered to rats for 13 and 31 days. This dose of isoproterenol (0.02 mg/kg once daily) was sufficient to cause a brief tachycardia and yielded significant myocardial weight gain.

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