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CARDIAC AND VASCULAR EFFECTS OF SYMPATHOMIMETIC DRUGS AFTER ADMINISTRATION OF TRI-IODOTHYRONINE AND RESERPINE

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In spinal cats treated with tri-iodothyronine, the effects of sympathomimetic drugs on cardiac contraction were diminished. Ouabain failed to restore the effects on the contractile force of the heart. The effects of sympathomimetic drugs on the force of contraction of papillary muscle were not reduced by tri-iodothyronine, but the threshold for induction of automaticity was lowered. There was no evidence that in cats treated with reserpine the sensitivity of peripheral vessels to sympathomimetic agents is decreased and that blood pressure changes are merely secondary to changes in cardiac contraction.

In 1961 Withrington & Zaimis published investigations on the cardiovascular effects of sympathomimetic agents in cats treated with reserpine. They used a mixture of pentobarbitone and chloralose to anaesthetize their animals, and recorded the venous outflow from a hind limb. They measured the force of cardiac contraction by a strain gauge arch attached to the left or right ventricle and recorded the arterial blood pressure. On the basis of their results Withrington & Zaimis (1961) came to the following conclusions: " In cats, 24 hr after the administration of 1 mg/kg of reserpine, it was found that (a) the heart is in failure; (b) the sensitivity of the peripheral vessels to adrenaline, noradrenaline and isoprenaline, administered intravenously or close-arterially, is decreased; (c) any blood pressure changes are, as a rule, secondary to changes in heart contraction; and (d) the peripheral blood flow passively follows the blood pressure changes."

As reserpine has been extensively used in the study of autonomic drugs, these results are of great significance and merit reinvestigation. In our experiments, cats anaesthetized with pentobarbitone and spinal cats were used. We measured the " femoral arterial inflow " using a Shipley-Wilson rotameter, the cardiac contractile force by a strain gauge arch attached to the right ventricle, and the systemic arterial blood pressure by a pressure transducer.

If the claim of Withrington & Zaimis that the pressor effects of sympathomimetic drugs after reserpine are due to stimulation of the heart is true, these drugs should have no such effect when cardiac stimulation is prevented. As dichloroisoprenaline blocks the chronotropic and inotropic actions of sympathomimetic drugs in anaesthetized dogs (Moran & Perkins, 1958), we investigated the effect of dichloroisoprenaline on the pressor action of sympathomimetic drugs in cats treated with reserpine.

Treatment with thyroid hormone reduced the action of sympathomimetic drugs on the force of cardiac contraction. If Withrington & Zaimis' hypothesis is true, one would expect that in animals treated with both thyroid hormone and reserpine the pressor effects of the sympathomimetic drugs would be reduced because their effects on the cardiac contractile force would be inhibited. We have therefore tested the effects of sympathomimetic drugs on animals treated in this way.

METHODS

Cats were anaesthetized with pentobarbitone sodium (30 mg/kg, intraperitoneally). Animals previously treated with reserpine received smaller amounts of the anaesthetic. Spinal cats were first anaesthetized with ether and their brains were destroyed after section of the cervical spinal cord. Their lungs were ventilated with a Harvard pump. The contractile force of the heart was measured with a Walton strain gauge arch attached to the right ventricle, the femoral arterial blood pressures with a Sanborn pressure transducer, and the heart rate from an electrocardiograph record. A Sanborn 150 recorder was used.

After giving heparin, a Shipley-Wilson rotameter (range 0 to 200 ml./min) was inserted into the abdominal aorta between the renal and iliac arteries. The lumbar arteries and one deep circumflex iliac artery were ligated, and the other circumflex iliac artery was cannulated for intra-arterial injections. Carotid arterial pressure, flow and contractile force were recorded on a Sanborn 150 recorder. The flow measured will be called "femoral arterial inflow." Stellate ganglia were stimulated by a Tektronix stimulator with rectangular pulses of supramaximal voltage at a frequency of 20 shocks/sec and of 1 msec duration.

Papillary muscles from the right ventricles of cats anaesthetized with ether were suspended in Tyrode solution at 38° C through which was bubbled a mixture of 5% carbon dioxide and 95% oxygen (v/v). The muscles were stimulated by rectangular pulses of 2 msec duration and supramaximal intensity at a frequency of 1 shock/sec. The contractions were recorded on a kymograph. Atria were dissected from the hearts of cats anaesthetized with ether and were suspended in Tyrode solution at 30° C. The contractions were recorded on a kymograph and the rate of beating was determined by counting during time intervals measured by stop-watch.

Reserpine (Serpasil, Ciba) was injected intraperitoneally on 1 or 2 days before the experiment, and tri-iodothyronine (Cytomel sodium, Smith, Kline & French, 0.2 to 0.4 mg/kg/day) was injected subcutaneously for 5 to 6 days. Dichloroisoprenaline (Eli Lilly, 5 mg/kg) and phenoxybenzamine (Dibenzyline, Smith, Kline & French, 5 mg/kg) were injected intravenously 30 min before a sympathomimetic agent was tested. Tyramine hydrochloride, (−)-adrenaline bitartrate, (−)-noradrenaline bitartrate monohydrate, and (−)-isoprenaline bitartrate dihydrate were used throughout these experiments and are referred to as tyramine, adrenaline, noradrenaline and isoprenaline respectively. They were made up in 0.9% saline, and injected intravenously unless otherwise stated; a femoral vein was used except in the flow studies, in which an external jugular vein was used.

RESULTS

The action of sympathomimetic drugs on spinal cats previously treated with tri-iodothyronine and/or reserpine

The effects of tyramine and noradrenaline on blood pressure, cardiac contractility and heart rate of spinal cats either treated or not with tri-iodothyronine are shown in Fig. 1. The effects both of tyramine and of noradrenaline on the force of cardiac contraction were reduced by the treatment, while the effects on the heart rate were not altered. The pressor effect of tyramine was reduced by treatment with tri-iodothyronine; that of noradrenaline was not significantly changed. The treated cats had a higher blood pressure and heart rate than the untreated animals.

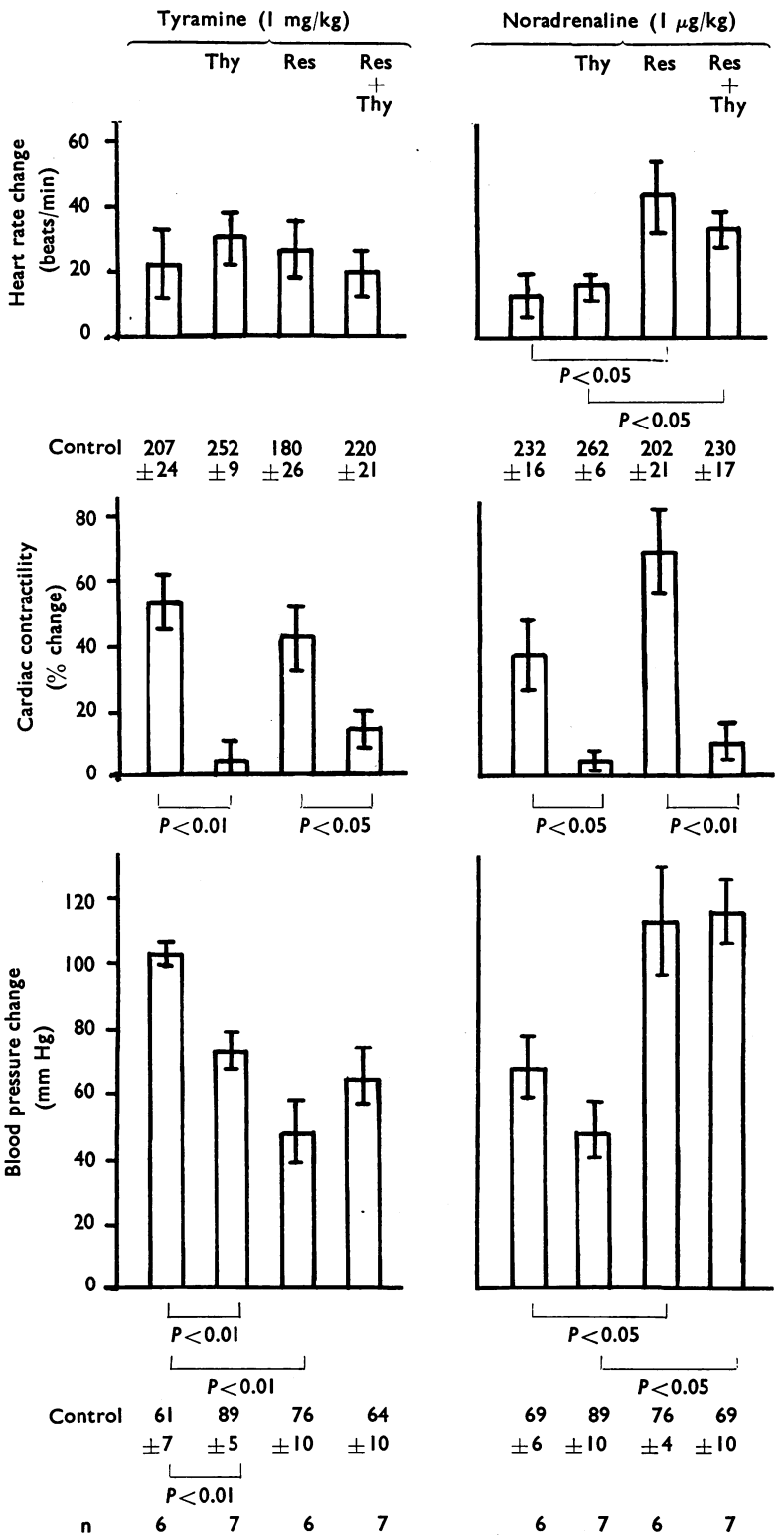

Fig. 1. Effects of tyramine and noradrenaline on heart rate, cardiac contractility and mean arterial blood pressure of spinal cats. The vertical bars represent standard errors of the means. n, number of experiments; Thy, tri-iodothyronine (0.2 to 0.4 mg/kg/day) injected subcutaneously for 5 to 6 days; Res, reserpine (0.25 mg/kg) injected intraperitoneally 1 day earlier. Controls are means±standard errors.

The effect of noradrenaline on the force of contraction in cats given both tri-iodothyronine (0.2 to 0.4 mg/kg/day) and reserpine (0.25 mg/kg, injected a day earlier) was smaller than in cats treated with reserpine alone, but the pressor effect was identical. This result demonstrates that in cats treated with reserpine noradrenaline can increase blood pressure without increasing the force of cardiac contraction. Reserpine also increased the pressor and chronotropic effects of noradrenaline and reduced the pressor effect of tyramine (Fig. 1).

In other experiments with animals treated with tri-iodothyronine the force of cardiac contraction was not increased by isoprenaline (1 μg/kg) and was only slightly increased by stimulation of a stellate ganglion. The effects on the heart rate of isoprenaline and of stimulation of stellate ganglion were not altered by treatment with tri-iodothyronine.

Ouabain (5 μg/kg, injected intravenously at intervals of 5 min) produced small increases in cardiac contraction but failed to restore the inotropic effects of the sympathomimetic drugs in cats treated with tri-iodothyronine.

In the isolated papillary muscle, prior administration of tri-iodothyronine (0.2 to 0.4 mg/kg/day) did not diminish the inotropic actions of tyramine, noradrenaline and isoprenaline (Table 1). However, automaticity frequently occurred.

TABLE 1

POSITIVE INOTROPIC ACTIONS OF TYRAMINE, NORADRENALINE AND ISOPRENALINE (PER CENT CHANGE±S.E.) AND OCCURRENCE OF AUTOMATICITY IN THE ISOLATED PAPILLARY MUSCLE OF THE CAT

The number of experiments is in parentheses or as the denominator of fractions. The magnitude of the increase in contraction is given only for experiments in which no automaticity occurred. When there were less than three experiments without occurrence of automaticity, individual results are listed. Automaticity was never seen in control muscles or in those treated with reserpine alone; its incidence in the remainder is given by the numerator of the subscribed fractions

	Tyramine		Noradrenaline		Isoprenaline	
Treatment	0.5 μg/ml.	2 μg/ml.	2 ng/ml.	8 ng/ml.	0.2 ng/ml.	0.8 ng/ml.
None	37±5 (4)	69±16 (4)	10±3 (4)	30±6 (4)	10±6 (4)	30±7 (4)
Reserpine (2×3 mg/kg/day)	7±2 (4)	8±2 (4)	6±2 (5)	22±4 (5)	7±4 (5)	23±2 (5)
Tri-iodothyronine (0·2 to 0·4 mg/kg/day)	37, 51 2/4	— 4/4	9±3 (3) 1/4	28±11 (3) 1/4	18±5 (3) 1/4	45, 59 2/4
Reserpine (0·25 mg/kg/day) and tri-iodothyronine (0·2 to 0·4 mg/kg/day)	2±1 (3) 0/3	3±2 (3) 0/3	12, 28 1/3	14, 44 1/3	11, 15 1/3	18, 33 1/3

The action of sympathomimetic drugs on anaesthetized cats previously treated with reserpine

The effects of tyramine, noradrenaline, adrenaline and isoprenaline on the blood pressure, cardiac contraction and heart rate of anaesthetized cats, and of cats treated with reserpine (3 mg/kg) on 1 or 2 days before the experiment, are shown in Fig. 2.

Phenoxybenzamine did not significantly inhibit the pressor effect of noradrenaline in cats treated with reserpine—an observation also made by Withrington & Zaimis (1961)—but led to a depressor effect of adrenaline. In cats treated with reserpine dichloroisoprenaline increased the pressor effect of adrenaline and led to a pressor

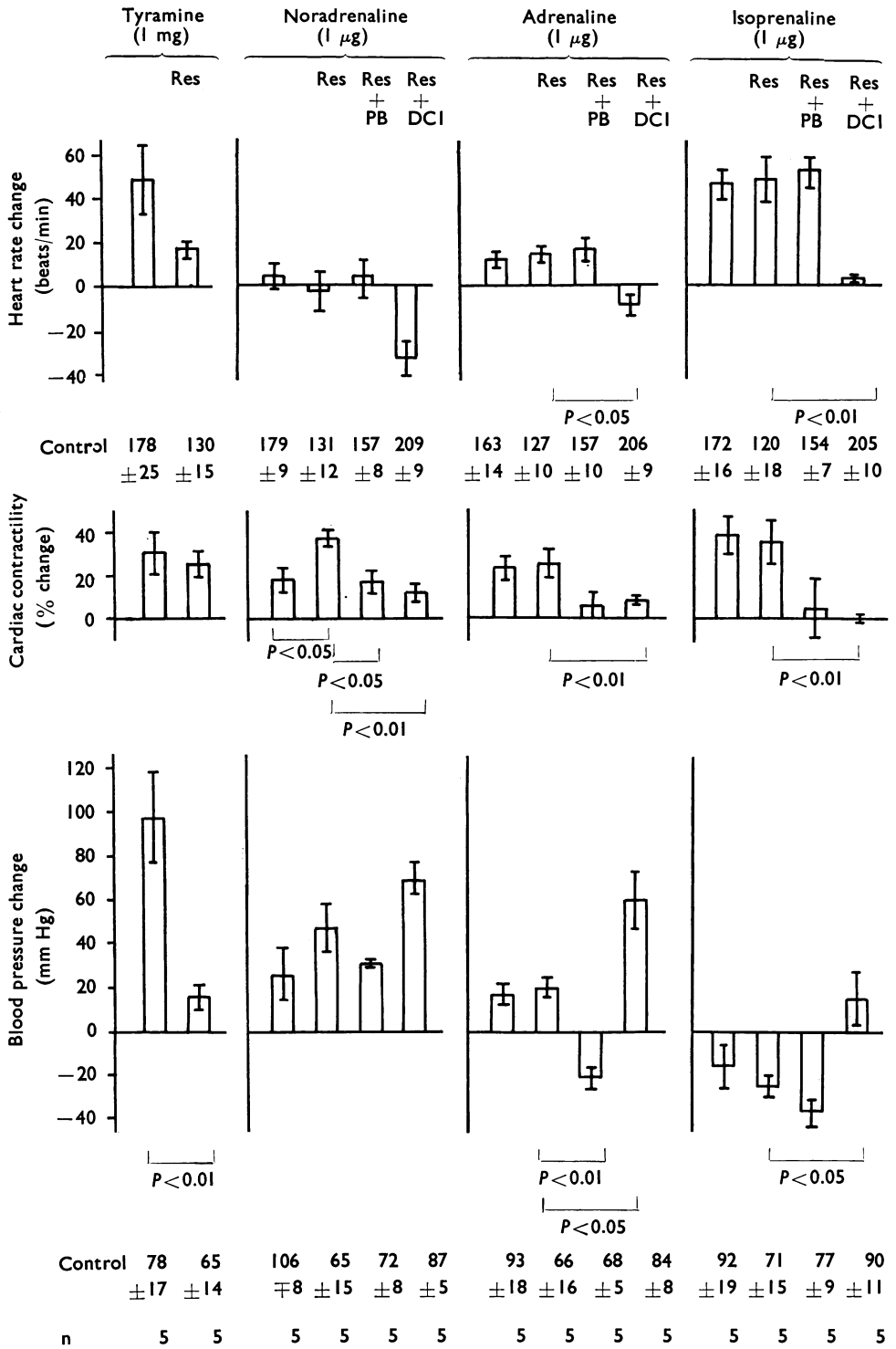

Fig. 2. Effects of tyramine, noradrenaline, adrenaline and isoprenaline on heart rate, cardiac contractility and blood pressure of cats anaesthetized with pentobarbitone. The vertical bars represent standard errors of the means. n, number of experiments; Res, reserpine (3 mg/kg) injected intraperitoneally on 1 or 2 days before the experiment; PB, phenoxybenzamine (5 mg/kg), and DCI, dichloroisoprenaline (5 mg/kg) injected intravenously at least 30 min before the sympathomimetic drugs.

effect of isoprenaline although it diminished the actions of adrenaline and isoprenaline on the heart. This result also suggests that the pressor effects of these drugs in cats treated with reserpine are not solely due to cardiac stimulation.

Reserpine (1 or 2 doses of 3 mg/kg) inhibited the inotropic action of tyramine on the papillary muscle (Table 1), but this effect was not observed in the anaesthetized cat (Fig. 2). The inotropic actions of noradrenaline and isoprenaline on the papillary muscle were slightly reduced by reserpine (Table 1) and the chronotropic actions on the atrium *in vitro* were slightly increased, but the differences were not significant.

When noradrenaline was injected intra-arterially there was a decrease in femoral arterial inflow, while when isoprenaline was injected the flow was increased (Fig. 3). When these compounds were injected intravenously the femoral arterial inflow at first followed passively the changes in systemic arterial blood pressure, being increased by a rise and decreased by a fall. Treatment with reserpine (1 mg/kg) did not alter

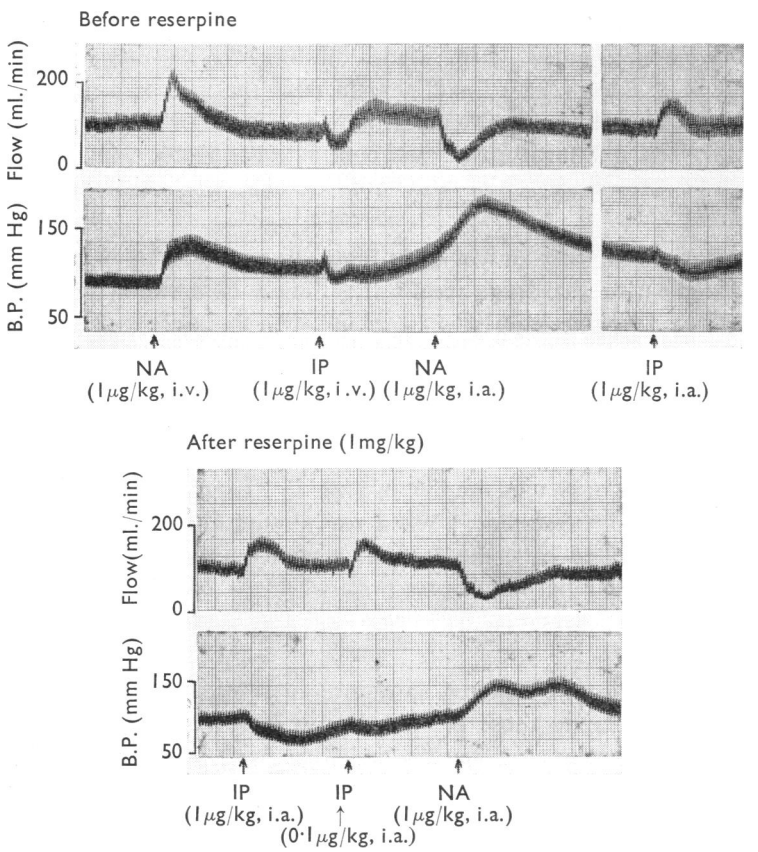

Fig. 3. Effects of noradrenaline (NA) and isoprenaline (IP) given intravenously (i.v.) or intra-arterially (i.a.) on the carotid arterial pressure (lower section of each record) and on blood flow in the abdominal aorta (upper section of each record) of cats anaesthetized with sodium pentobarbitone. Doses are given in μg/kg. Upper record, untreated cat; lower record, cat treated with reserpine (1.0 mg/kg).

these responses. A reduction of flow following intra-arterial injection of noradrenaline and an increase in flow following intra-arterial isoprenaline was observed in all six cats treated with reserpine.

Similar experiments on the femoral arterial inflow have also been carried out in cats treated with tri-iodothyronine; the treatment did not alter the vascular responses. In three experiments on cats treated with tri-iodothyronine, the mean femoral arterial inflow (ml./min$\pm$s.e.) was 96$\pm$32, in six untreated cats 76$\pm$8, and in six cats treated with reserpine 60$\pm$16 ml./min.

DISCUSSION

Sympathomimetic drugs did not increase cardiac contraction in spinal cats treated with tri-iodothyronine. This result suggests that the myocardium is in a state of exhaustion. Our observations that heart rate and systemic blood pressure were elevated support this view. Thomas (1957) concluded similarly: "This entails an increased volume of cardiac output per minute, increased rate of work by the heart, and ultimate embarrassment of the myocardium." On the other hand, Brewster, Isaacs, Osgood & King (1956) found that in dogs the inotropic and chronotropic actions of adrenaline and noradrenaline were increased by feeding thyroid gland. These workers did not measure cardiac contraction directly. In our experiments treatment with tri-iodothyronine did not increase the chronotropic effect of noradrenaline.

The fact that ouabain had only a slight inotropic action and was unable to restore the inotropic effect of the drugs recalls the clinical observation that heart failure in thyrotoxicosis responds poorly to treatment with digitalis.

Our method of measuring sympathomimetic effects on peripheral blood flow differs from that of Withrington & Zaimis (1961). We measured the flow in the lower abdominal aorta (femoral inflow) and they the venous outflow from a hind limb. On injecting noradrenaline (10 μg intravenously) Withrington & Zaimis observed a reduction in venous outflow in untreated cats and an increase in outflow in animals treated with reserpine. When we injected noradrenaline (1 μg/kg intravenously) into untreated cats, the femoral arterial inflow increased together with the rise in systemic arterial blood pressure; when the systemic blood pressure fell following injection of isoprenaline (1 μg/kg intravenously), the femoral arterial inflow decreased.

When these drugs were injected intra-arterially into untreated cats we again obtained results similar to those of Withrington & Zaimis; noradrenaline causing a decrease and isoprenaline an increase in blood flow. But, whereas Withrington & Zaimis found noradrenaline and isoprenaline to have no effect when injected intra-arterially into cats treated with reserpine, we found that noradrenaline and isoprenaline produced their usual effects: a reduction in arterial inflow after noradrenaline and an increase after isoprenaline.

It thus appears that sympathomimetic drugs can act directly on peripheral blood vessels of cats treated with reserpine. This conclusion is substantiated by our results with dichloroisoprenaline and tri-iodothyronine. Dichloroisoprenaline reduced the

actions of noradrenaline and isoprenaline on the force of contraction and the rate of the heart in cats treated with reserpine without diminishing the pressor effect of noradrenaline (Fig. 2). Tri-iodothyronine inhibited the action of noradrenaline on the force of cardiac contraction but did not diminish the pressor effect of the drug in cats treated with reserpine (Fig. 1).

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