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INCREASE IN NORADRENALINE CONTENT OF TISSUES AFTER INFUSION OF NORADRENALINE, DOPAMINE AND L-DOPA

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The responses to tyramine and to sympathetic stimulation are reduced or abolished when the noradrenaline content of the tissues has been depleted by reserpine treatment (Carlsson, Rosengren, Bertler & Nilsson, 1957). They are restored after an infusion of noradrenaline (Burn & Rand, 1958, 1960*a*), or infusion of precursors of noradrenaline, such as dopamine (*β*-3: 4-dihydroxyphenylethylamine) and L-DOPA (Burn & Rand, 1960*b*). These observations led to the suggestions that it is the store of noradrenaline in a tissue which is necessary for the response to tyramine and that the size of the store determines the magnitude of the response to sympathetic stimulation. Our purpose in the present paper has been to determine the effect of infusions of noradrenaline, dopamine and L-DOPA in increasing the store of noradrenaline in organs of normal and reserpine-treated cats.

METHODS

Spinal cats (2·5–3·5 kg) were prepared by Dale's method as described by Burn (1952). Evisceration was performed by dividing the following structures between ligatures: rectum, inferior and superior mesenteric arteries, coeliac axis, oesophagus, portal vein and bile duct. Blood pressure was recorded from one carotid artery and a 1 mm polythene tube was placed in the other carotid artery to withdraw blood samples. The right kidney was dissected free from fat and removed after ligating the vessels at the hilum. In female cats one horn of the uterus was tied close to the fundus and the horn was removed after ligating the ovarian artery and vein. A sample of 5–6 ml. of blood was withdrawn into a polythene centrifuge tube containing 100 u. heparin. Noradrenaline (1 mg), dopamine (25 mg) or L-DOPA (25 mg) was infused into a small vein in the foreleg from a continuous slow-injection syringe (C. F. Palmer Ltd.). Each drug was given in 14·3 ml. of 0·9 % NaCl adjusted to pH 4–5 and was infused during 40 min. The infusion apparatus was then disconnected and after a further 20 min had elapsed the left kidney and the other uterine horn were removed and a second blood sample was taken. At this time the blood pressure had fallen from the level attained at the end of the infusion and had remained at a low steady value for 10–15 min.

The blood samples were centrifuged for 10 min at 5000 rev/min immediately after collec-

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tion and the decanted plasma stored at −10° C until required for assay. The capsule was removed from the kidney and the uterus freed from connective tissue. These organs were dried between filter papers, weighed, and stored in the deep freeze. The total time which elapsed between removal of the organs and placing them in the deep freeze was 10 min. To determine the noradrenaline content of tissues they were extracted in 5 ml. of saline/g by the method described by Burn & Rand (1959) and assayed on the blood pressure of the pithed rat, recorded by inserting into the carotid artery a polythene tube connected to a strain-gauge pressure transducer (Statham Laboratories type P 23 Db). The output from the transducer bridge circuit was fed into a DC amplifier connected to an ink-writing recorder.

Cats were treated with reserpine by intraperitoneal injection of 3–4 mg of reserpine dissolved in 20 % ascorbic acid on each of two days and were used for experiment on the third day.

Observations were made on the response of the cat's uterus to hypogastric nerve stimulation as described by Burn & Rand (1960*b*).

RESULTS

Assay of noradrenaline

Previous experience with the assay of organ extracts for noradrenaline on the blood pressure of the pithed rat has been virtually without complications arising from the presence of interfering pressor substances other

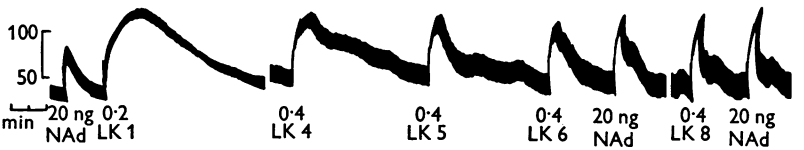

Fig. 1. Rat blood pressure recorded with a transducer manometer. LK 1–8, effect of successive injections of a left kidney extract, showing tachyphylaxis. LK 1, first injection (0·2 ml., i.e. ≡ 40 mg) produced a pressor response greatly exceeding in amplitude and duration that due to 20 ng noradrenaline (NAd). The 8th injection (LK 8, 0·4 ml.) produced a response virtually indistinguishable in form from that due to 20 ng noradrenaline. Pressure calibrations in mm Hg.

than noradrenaline. This was not the case when we injected extracts of kidney. The first injection of kidney extract into a pithed rat resulted in a large and prolonged rise of blood pressure. With subsequent injections of the kidney extract this slow pressor response became less and less marked and when the 4th–8th injections were given the blood pressure response was indistinguishable in form from that to an 'equi-pressor' dose of noradrenaline. Thus in Fig. 1 the first injection of 0·2 ml. of kidney extract (equivalent to 40 mg of kidney) produced a larger and longer-lasting response than 20 ng noradrenaline. However, the response to the 8th injection of the same extract (0·4 ml., equivalent to 80 mg of kidney) showed a complete tachyphylaxis to the slow pressor component and was now virtually indistinguishable from the response to 20 ng noradrenaline. After desensitizing the rat to the slow pressor component of the kidney extract we have regularly observed in these experiments a larger response

to noradrenaline. Our mean value for the noradrenaline content of normal cat's kidney was 196 ng/g (16 experiments, range 125–325 ng/g), which is very close to the figures published by von Euler (1956) who found a mean of 210 ng/g (4 experiments, range 110–320 ng/g). No difficulties were experienced in the assay of the noradrenaline content of plasma or of uterine extracts.

Increase in noradrenaline content after infusing noradrenaline

All the experiments with infusions of noradrenaline were carried out on eviscerated cats. In two preliminary experiments it was found that the noradrenaline content of a kidney removed immediately after preparing the cat was the same as the content in the second kidney removed 75 min later.

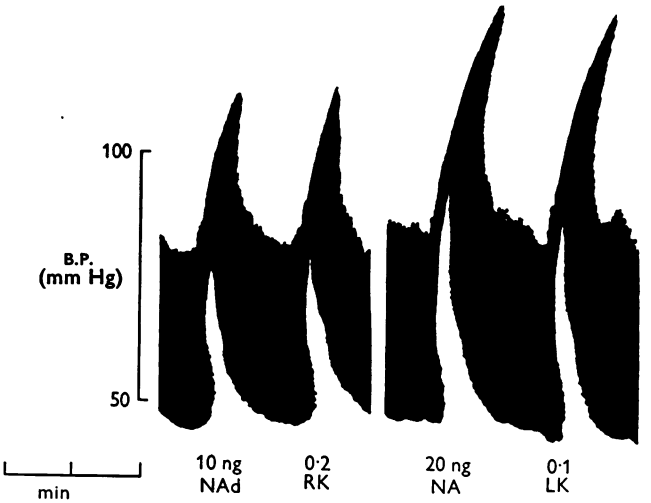

Fig. 2. Rat blood pressure. Uptake of noradrenaline by kidney from infusion of 1 mg noradrenaline. RK, response to 0·2 ml. of an extract of the right kidney (removed from the cat before infusion), equal to 10 ng noradrenaline (NAd). LK, 0·1 ml. of a similarly prepared extract of the left kidney, removed from the cat 20 min after the infusion.

The estimation of the pressor activity of extracts of kidneys taken from the same cat before and after the infusion of noradrenaline is illustrated in Fig. 2. In this experiment 0·1 ml. of the kidney extract made after the infusion had twice the potency of 0·2 ml. of control kidney extract; this represents a fourfold increase in content of noradrenaline.

The noradrenaline contents of the kidneys, uterine horns and blood plasma before and after the infusion of 1 mg of noradrenaline into both reserpinized and untreated cats are given in Table 1. In one untreated cat there was no increase in the noradrenaline content of the uterus and in

another neither the kidney nor the uterus took up noradrenaline from the infusion; it is interesting to note that the initial noradrenaline contents of these organs were the highest that were observed in this series of experiments. Uptake of noradrenaline was observed in every kidney and uterus of reserpine-treated cats. However, the mean figures for the content of noradrenaline in kidney and uterus after the infusion were lower in reserpine-treated than in normal cats. This observation suggests that reserpine treatment may inactivate part of the binding mechanism for noradrenaline.

TABLE 1. Noradrenaline content of kidney, uterus (ng/g) and plasma (ng/ml.) before and after infusing 1 mg noradrenaline

Kidney			Uterus			Plasma		
Before	After	Increase	Before	After	Increase	Before	After	Increase
A. Untreated, eviscerated cats								
188	250	62	—	—	—	—	—	—
250	500	250	1250	1250	0	—	—	—
162	325	163	500	1000	500	—	—	—
125	312	187	325	450	125	25	38	13
250	1000	750	625	1000	375	25	68	43
275	275	0	750	750	0	30	45	15
Means								
208	444	235	690	890	200	27	50	23
B. Reserpine-treated, eviscerated cats								
63	175	112	50	188	138	33	33	0
75	200	125	38	188	150	25	38	13
250	750	500	188	253	65	75	75	0
150	250	100	100	188	88	38	100	62
Means								
135	345	210	94	204	110	43	57	14

The plasma pressor activity 20 min after the end of the infusion was raised in both normal and reserpine-treated cats. However, this increase in plasma noradrenaline could only contribute a very small part of the increases seen in the kidney and uterus.

The noradrenaline content of the uterus and the kidney was clearly increased after infusing 1 mg noradrenaline into cats. Raab & Gigee (1955, 1958) found that after the intraperitoneal injection of noradrenaline 10 mg/kg into dogs there was a mean increase of noradrenaline of 1·4 μg/g heart muscle and that the total catecholamine content of blood vessels (measured colorimetrically) was increased. However, von Euler (1956) stated that he could not significantly alter the catecholamine content of heart, spleen, liver, kidney or skeletal muscle of the cat by an intravenous infusion of 0·5 mg noradrenaline or by 1–2 mg/kg intraperitoneally. He considered that the results of Raab & Gigee were due to the use of massive doses (10 mg/kg intraperitoneally). The doses of noradrenaline used by us (7·1–10 μg/kg/min) were similar to von Euler's (2·5–7·8 μg/kg/min).

The estimation of plasma pressor activity in terms of noradrenaline in the pithed rat gave values which are higher than those generally accepted. However, it can be noted that Brown & Gillespie (1957) and Brown, Davies & Gillespie (1958), who used a similar procedure

for estimating plasma noradrenaline, published figures which are in accord with our results. Plasma from reserpine-treated cats had a higher pressor activity (in terms of noradrenaline). Muscholl & Vogt (1957) found an increase in the adrenaline level of plasma of rabbits after treating them with reserpine.

Infusion of dopamine

The results of infusing 25 mg dopamine into reserpinized and untreated eviscerated cats are given in Table 2. The extracts of the organs taken after the infusion gave an increased pressor activity on the pithed rat in only 1 out of 5 experiments with the normal kidney and in 3 out of 5 experiments with the normal uterus after the infusion of dopamine. Reserpine-

TABLE 2. Noradrenaline equivalent of kidney, uterus (ng/g) and plasma (ng/ml.) before and after infusing 25 mg dopamine

Kidney			Uterus			Plasma		
Before	After	Increase	Before	After	Increase	Before	After	Increase
			A. Normal, eviscerated cats					
200	200	0	250	250	0	25	40	15
188	188	0	188	250	62	38	38	0
125	125	0	375	375	0	25	59	24
300	625	325	1200	1300	100	25	90	65
188	188	0	200	262	62	25	75	50
Means								
200	265	65	443	487	44	28	60	31
			B. Reserpine-treated, eviscerated cats					
100	150	50	0	50	50	38	38	0
175	438	263	—	—	—	50	38	−12
150	250	100	100	188	88	38	100	62
112	112	0	188	313	125	18	58	40
75	125	50	38	63	25	13	38	25
Means								
122	215	93	82	154	72	31	54	23

treated cats more regularly showed an increase in noradrenaline content; uptake was observed in the kidney in 4 out of 5 experiments, and in the uterus in 4 of 4 experiments.

With our methods it was not possible to say directly whether the pressor activity on the pithed rat of the extracts made from the kidney and uterus after dopamine infusion was due to unchanged dopamine or to noradrenaline, which has served as the assay standard. In our hands dopamine has 1/200th of the pressor action of noradrenaline in the pithed rat (cf. 1/150, Vogt, 1959; 1/80, Muscholl, 1959). We observed a mean increase of 93 ng/g in the noradrenaline equivalent of reserpine-treated kidneys following dopamine infusion. If all the increased pressor activity were due to unchanged dopamine this would represent an uptake of 18·6 μg dopamine/g tissue. The most likely possibility is that part of the increase

in the pressor activity of the tissue extract was attributable to noradrenaline and part to unchanged dopamine.

Restoration of hypogastric nerve effect in reserpine-treated cats

Burn & Rand (1960*b*) have shown that an infusion of noradrenaline enhances the inhibitory response of the uterus to stimulation of the

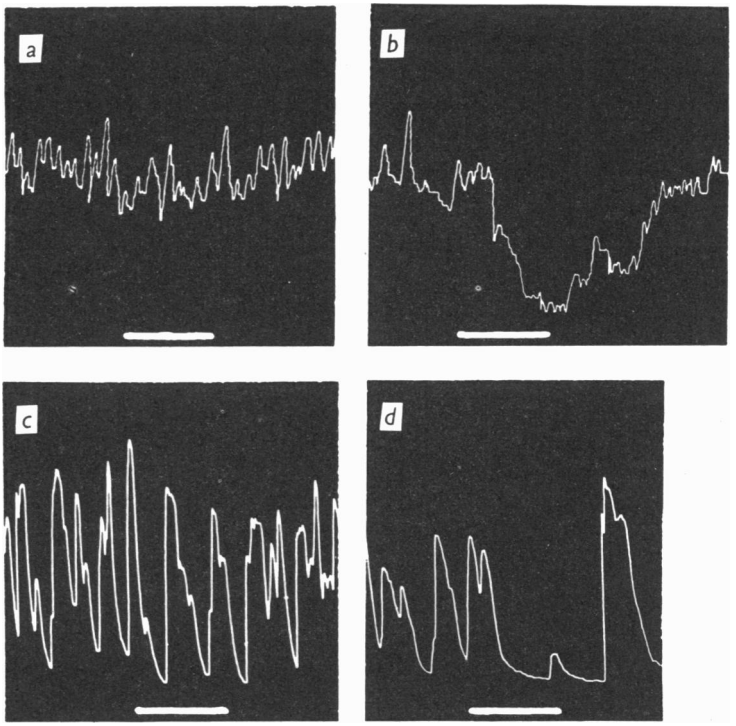

Fig. 3. *In situ* record of uterine movements in a reserpine-treated cat. Upper and lower records are from two separate experiments. The horizontal lines indicate stimulation for 2 min of the hypogastric nerve with square waves of 1 msec duration and 25 V amplitude at 20/sec. The inhibitory response to sympathetic nerve stimulation was restored by an infusion of 1 mg noradrenaline between (*a*) and (*b*), and of 25 mg dopamine between (*c*) and (*d*).

hypogastric nerve. Similarly an infusion of dopamine into a reserpine-treated cat restored the uterine response to hypogastric nerve stimulation (Fig. 3*d*). It is difficult to assess the relative efficacy of 1 mg noradrenaline and 25 mg dopamine in restoring the uterine response in reserpine-treated cats, since this response depends on the pattern of uterine activity. The upper portion of Fig. 3 shows a uterus with a rapid rhythm and a high tone. At first, stimulation had no effect, but 30 min after 1 mg noradrenaline

had been infused hypogastric nerve stimulation produced a decrease in tone (*b*). The lower records show another experiment in which the uterus had a slow rhythm of large amplitude which was not affected by nerve stimulation at first, but after infusion of 25 mg dopamine hypogastric stimulation resulted in an inhibition of rhythm (*d*).

Infusion of L-*DOPA*

Four experiments were carried out in which 25 mg of L-DOPA was infused during 40 min into eviscerated cats, two of which were untreated and two reserpine-treated. In no experiment was there any increase in the

TABLE 3. Noradrenaline content of kidney, uterus (ng/g) and plasma (ng/ml.) before and after infusing 25 mg L-DOPA

Kidney			Uterus			Plasma		
Before	After	Increase	Before	After	Increase	Before	After	Increase
			A. Normal, uneviscerated cats					
325	325	0	500	500	0	25	75	50
188	376	188	415	415	0	5	18	13
125	125	0	250	375	125	10	10	0
Means		63			42			21
			B. Reserpine-treated, uneviscerated cats					
125	188	63	63	125	62	30	40	10
175	225	50	50	92	42	13	13	0
88	63	−25	31	31	0	—	—	
Means		29			35			5

extractable pressor activity of kidney or uterus although the plasma activity was slightly increased. Six further experiments with L-DOPA were carried out on cats which were not eviscerated (3 untreated, 3 reserpine-treated). Uptake of noradrenaline was demonstrable in 4 cats (Table 3).

The spleens were removed from intact cats at the end of the experiment after infusing L-DOPA, and assayed for noradrenaline. The noradrenaline content of spleens after infusing L-DOPA, and noradrenaline content of spleens taken from cats at evisceration are given below:

Normal cat	1·0 μg/g
Normal cats after infusing 25 mg L-DOPA	0·875, 1·0 μg/g
Reserpine-treated cat	0·063 μg/g
Reserpine-treated cats after infusing 25 mg L-DOPA	0·375, 0·027, 0·213 μg/g

The values for the noradrenaline content of spleens from normal and reserpine-treated cats are in accord with those obtained elsewhere using identical methods (Burn & Rand, 1959). The infusion of L-DOPA did not increase the noradrenaline content of spleen from normal cats, but in 2 out of the 3 reserpine-treated cats the noradrenaline content was increased, by the infusion of L-DOPA, to 178 and 312 % of the mean value for reserpine-treated spleens. Von Euler & Uddén (1951) reported that the infusion of 5·2 mg of L-DOPA to 32 mg DL-DOPA

approximately doubled the noradrenaline content of the spleen, heart and liver. In their experiments the organs were removed immediately at the end of the infusion, whereas in ours 20 min elapsed.

It was apparent from these results that the presence of the abdominal viscera was necessary if the infusion of L-DOPA was to lead to an increase in the noradrenaline content of the tissues. We have examined this in the following way. Burn & Rand (1960*b*) showed that in reserpine-treated rats, in which the response to tyramine was small, an infusion of L-DOPA led to an increase in the response to tyramine. If the restored response to tyramine were due to a restoration of the noradrenaline content of the tissue, there should be a difference in the effect of an infusion of L-DOPA on the subsequent response to tyramine in non-eviscerated and eviscerated reserpine-treated cats. Two experiments were carried out to investigate this point. In both uneviscerated and eviscerated cats the infusion of noradrenaline led to an enhancement of the response to tyramine. In an uneviscerated cat there was a slight, but quite definite, increase in the response to tyramine after the infusion of L-DOPA, and this enhanced response was still seen for the third injection of tyramine after the infusion. On the other hand, in an eviscerated cat the infusion of L-DOPA brought about only a barely perceptible increase in the response to tyramine and the second injection of tyramine was again without action.

The infusion of L-DOPA at the rate of 25 mg in 40 min increased the blood pressure of the reserpine-treated uneviscerated cats. In four experiments the maximum blood pressure rises were 84, 80, 24 and 20 mm Hg. In reserpine-treated, eviscerated cats and in untreated cats L-DOPA had no pressor action. Clark (1959) states that complete evisceration usually decreases the response to L-DOPA, but not always.

DISCUSSION

The mean uptake of noradrenaline from an infusion of 1 mg was approximately 0·2 μg/g of tissue. In our experiments the cats were made spinal and eviscerated, and one kidney was removed before the infusion. The mean weight of the remaining kidney and uterus was 10 g, which would account for 2 μg of the noradrenaline infused. If one allows a weight of 20 g for the remaining sympathetically innervated structures (heart, lungs, blood vessels, etc.), and the same uptake per gram of tissue, we can still only account for 6 μg noradrenaline, or 0·6 % of the quantity infused. Axelrod, Weil-Malherbe & Tomchick (1959) have studied the location of ^{3}H-labelled adrenaline in tissues, following its infusion into the cat. From their data it is apparent that the sympathetically innervated tissues store only a small percentage of the total amount of adrenaline infused, although in whole mice about 30 % of unchanged adrenaline was still present in the

body 20 min after an intravenous injection. Goodall, Kirshner & Rosen (1959) found that in man radioactivity corresponding to 11 % of ^{14}C-labelled noradrenaline appeared in the urine in the first hour after an infusion and 67 % was recovered in 24 hr. They suggest that tissue cells pick up noradrenaline, store it as a complex and gradually release it for metabolism, a conclusion also reached by Axelrod *et al.* (1959). There are at least two possibilities to reconcile this suggestion with the low percentage of infused noradrenaline which we found in tissues. First, that inactive metabolites may also be bound in tissues, as Axelrod *et al.* found for 3-O-methyladrenaline, and secondly, that the complex of noradrenaline in the tissue stores may not be readily split to yield biologically active noradrenaline by the mild extraction procedures we used.

The infusion of dopamine into the cats used in these experiments produced approximately the same response on the blood pressure as the infusion of noradrenaline at 1/25th of the dose. Burn & Rand (1960*b*) have shown in reserpine-treated cats that dopamine infusion will restore the pressor response to tyramine and the dilatation of the pupil. From examination of their figures (Figs. 2 and 6 in Burn & Rand, 1960*b*) it appears that the restoration produced by dopamine is roughly equivalent to that produced by 1/20th of the dose of noradrenaline.

Burn & Rand (1960*b*) showed that L-DOPA infusion restored responses to sympathetic nerve stimulation and to tyramine when these were ineffective after reserpine treatment, and that the restoration was longer lasting than that following a noradrenaline infusion. We found that an infusion of L-DOPA produced a relatively small increase in the noradrenaline content of the tissues, which could serve to restore the response of the tissue, but if in addition the infusion provided a reserve of the precursors of noradrenaline in the tissues available for further synthesis, we can understand why the restoration was longer-lasting than that produced by a noradrenaline infusion.

The infusion of L-DOPA increased the content of noradrenaline in tissues (kidney, uterus, spleen) in 2 out of 8 experiments in intact normal cats and in 6 out of 8 experiments in intact reserpine-treated cats. The smaller uptake observed in noradrenaline content in normal cats may be the result of suppression of synthesis; when the noradrenaline content of the tissue is reduced by reserpine treatment, synthesis may proceed more readily. The smaller increase in noradrenaline content of normal cat's tissue compared with reserpine-treated cats following dopamine infusion can be understood in the same way.

Our results indicate that the abdominal viscera must be intact if the infusion of L-DOPA is to produce a deposition of tissue stores of noradrenaline. Holtz (1959) states that high concentrations of DOPA decarboxylase

are found in kidney, liver, pancreas and intestine. In our evisceration experiments the pancreas and intestines were removed, and the liver was deprived of both its portal and hepatic blood supply. The kidney which remained in the circulation during the infusion was apparently not a sufficiently active source of DOPA decarboxylase to lead to an increase in the noradrenaline content of tissue, nor indeed to convert enough DOPA into a pressor metabolite.

SUMMARY

1. The infusion of 1 mg of noradrenaline into reserpine-treated or untreated eviscerated cats led to an increase in the noradrenaline content of the kidney and uterus.

2. The infusion of 25 mg of dopamine into cats increased the pressor activity of extracts of kidney and uterus on the blood pressure of pithed rats.

3. The lack of response of the uterus of the reserpine-treated cat to hypogastric nerve stimulation was corrected by infusion of dopamine.

4. The infusion of 25 mg of L-DOPA increased the noradrenaline-equivalent of kidney, uterus and spleen of reserpine-treated cats when they were not eviscerated. L-DOPA was pressor in these cats and enhanced the impaired pressor response to tyramine. In eviscerated cats L-DOPA did not increase the noradrenaline equivalent of tissues, was not pressor, and did not enhance the response to tyramine.

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