In Table 1 are shown the mean values for metyrapone and reduced metyrapone measured in the urine of the 9 patients undergoing the metyrapone test. Both compounds were excreted mainly as the glucuronides. Reduced metyrapone occurred in appreciably larger amounts than metyrapone, particularly on Day 2 when little change was seen in the level of reduced metyrapone, but the level of metyrapone fell markedly. Small but significant quantities (108 mg $\pm$ 14·9 s.e.) of reduced metyrapone could still be detected on Day 3. The mean quantity of metyrapone plus reduced metyrapone recovered from the urine on Days 1–3 was 1·97 g $\pm$ 0·13 s.e.

Reduced metyrapone is quantitatively an important metabolite of metyrapone. It is not an inactive metabolite, being as potent an inhibitor of ox and human adrenal 11β-hydroxylase as metyrapone (Sprunt & Hannah, 1968).

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Alterations in noradrenaline turnover in the peripheral sympathetic neurons induced by stress

It has long been known that injected noradrenaline can be taken up and concentrated in peripheral sympathetic nerves (Whitby, Axelrod & Weil-Malherbe, 1961; Hamberger, Malmfors & others, 1964). Furthermore, noradrenaline incorporation is greatest in tissues with rich sympathetic innervation (Kopin, 1966). In addition to the normal endogenous noradrenaline content, the uptake of noradrenaline into tissues after intravenous injection is related to the proportion of cardiac output delivered to the tissue. Endogenous transmitter and exogenously given tritiated noradrenaline (^{3}H-NA) can be released by nerve impulses which, together with other evidence, indicate that the latter is present in the same store as the endogenous catecholamine (Iversen, 1967). Thus, the disappearance rate and the impulse flow seems to be correlated. I now report the influence of various stress conditions, which might increase sympathetic tone, on the disappearance rate of administered ^{3}H-NA.

Male albino rats were injected with ^{3}H-NA 1 μg/kg, i.v., 3 h before stress was induced. The animals were stressed for 3 h and then killed by exsanguination under light chloroform anaesthesia. Various peripheral organs were dissected and homogenized with an "Ultra-Turrax" apparatus in ice cold 0·4 N perchloric acid. After centrifugation, filtration and neutralization, the samples were passed through Dowex 50 cation-exchange columns from which the noradrenaline was eluted (Carlsson & Waldeck, 1963). The ^{3}H-NA content was measured by liquid scintillation counting technique (Waldeck, 1968).

Three different kinds of stress were investigated, (1) cold stress, (2) stress induced by electric shock, (3) immobilization stress. For (1) the rats were shaved the day before the experiment under light ether anaesthesia. They were maintained at an environmental temperature of +3–4° for 3 h. The rectal temperature was +32–35° at

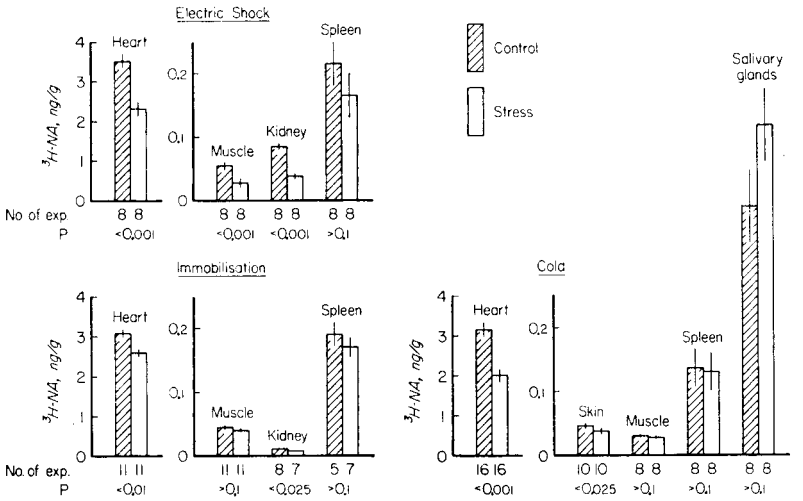

FIG. 1. The effect of different stress conditions on the disappearance rate of ^{3}H-NA from tissues. All values are 6 h after the i.v. injection of ^{3}H-NA. The stress was induced between 3 and 6 h after the injection. The vertical bars on top of the columns indicate s.e. *P* values are calculated by analysis of variance (q × q equatorial test, Winer, 1962).

death. The animals had a hunched back posture during the experiment. For (2) the shocks were given in commercially-available rat behavioural chambers containing a grid floor connected to a stimulator. Each rat was stressed for six periods of 10 min altering with rest periods of 20 min for a total of 3 h. During the 10 min stimulation period, each animal received 400 shocks of 1·6 mA intensity and 0·5 s duration. For (3) the rats were in small wire cages (Corrodi, Fuxe & Hökfelt, 1967) for 3 h.

Table 1. *Content of* ^{3}H-NA, ng/g, *in various rat tissues* 3 *and* 6 *h after injection of* ^{3}H-NA (1 mg/kg, i.v.). Values are means ± s.e.

	3 h	6 h	*P* value	Statistical test used
Heart	4·72 ± 0·40 n = 6	3·72 ± 0·35 n = 8	>0·10	analysis of variance
Spleen	0·33 ± 0·022 n = 6	0·24 ± 0·021 n = 4	<0·05	*t*-test
Kidney	0·18 ± 0·018 n = 6	0·11 ± 0·016 n = 8	<0·005	analysis of variance
Muscle	0·049 ± 0·0381 n = 6	0·045 ± 0·0330 n = 8	>0·10	analysis of variance

Table 2. ^{3}H-NA *in various rat tissues in control and electroshock stressed animals.* Comparison is made between untreated animals and animals pretreated with phenoxybenzamine (10 mg/kg, i.p.) and propranolol (10 mg/kg, i.p.). Values are means ± s.e., the number of animals being 8 in all cases; s.e. values are calculated by analysis of variance (p × q equatorial test, Winer, 1962).

	No drug			Phenoxybenzamine + propranolol		
	Control ng/g	Stress ng/g	Stress as % of control	Control ng/g	Stress ng/g	Stress as % of control
Heart	3·51 ± 0·183	2·30 ± 0·183	65·0 ± 7·38	2·32 ± 0·133	1·61 ± 0·133	69 ± 8·1
Kidney	0·08 ± 0·005	0·04 ± 0·005	44·0 ± 8·33	0·07 ± 0·008	0·04 ± 0·008	59 ± 15·3
Spleen	0·22 ± 0·035	0·17 ± 0·035	77 ± 22·28	0·11 ± 0·008	0·66 ± 0·008	55 ± 10·3
Muscle	0·05 ± 0·008	0·03 ± 0·008	50 ± 20·37	0·02 ± 0·002	0·01 ± 0·002	75 ± 17·7

In control experiments there was only a slight decrease of the ^{3}H-NA content in heart, spleen, kidney and muscle of the hind leg, during the period 3–6 h after administration of ^{3}H-NA (Table 1). In the cold stress experiments there was a decrease in the ^{3}H-NA content of the heart ($P < 0{\cdot}001$) and skin ($P < 0{\cdot}025$) compared to the corresponding organs of control animals, but there was no accelerated disappearance of ^{3}H-NA in the muscle of the hind leg, kidney and spleen ($P > 0{\cdot}1$). In the electric shock experiment there was an accelerated disappearance of ^{3}H-NA in the heart, kidney and muscle of the hind leg ($P < 0{\cdot}001$) but not in the spleen ($P > 0{\cdot}1$). In the immobilization stress experiments, it was possible to show a somewhat accelerated disappearance of ^{3}H-NA from the heart ($P < 0{\cdot}01$) and kidney ($P < 0{\cdot}025$) but not from the spleen and muscle of the hind leg (Fig. 1).

These experiments show that stress factors can increase the disappearance rate of ^{3}H-NA from tissues which, however, may be influenced differently by various types of stress.

The accelerated ^{3}H-NA turnover seen in many of the organs investigated might reflect an increased impulse flow in the sympathetic nerves evoked by the different stress factors. However, other factors that could influence the disappearance rate of the given ^{3}H-NA must be kept in mind. For example, it is known that a decrease in blood flow caused by vasoconstriction may diminish the elimination of the released transmitter via the blood (Rossell, Kopin & Axelrod, 1963). Conversely, blood flow may be increased by activation of the tissue causing an increased disappearance rate of noradrenaline (Carlsson, Folkow & Häggendal, 1964). Experiments were designed to minimize the circulatory effects of vascular reflexes after activation of the sympathetic nervous system. Therefore, animals were given an α- and a β-receptor blocking agent (phenoxybenzamine, 10 mg/kg; propranolol, 10 mg/kg). After this treatment the animals showed a pronounced ptosis. The treatment accelerated the disappearance of ^{3}H-NA from tissues. Moreover, the stress factor investigated (electric shocks) still caused an acceleration of disappearance of ^{3}H-NA as in the experiments with untreated animals (see Table 2). It is thus likely that stress, at least that induced by electric shocks, increases noradrenaline turnover in the peripheral adrenergic system by increasing nerve impulse flow.

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