Noradrenaline turnover in renal hypertensive rats

Various types of experimental hypertension are thought to be associated with alterations in the metabolism of catecholamines. Thus, the levels of endogenous noradrenaline were reduced and the fall in specific activity after injection of [^{3}H]noradrenaline was greater and more prolonged in the hearts of rats made hypertensive with desoxycorticosterone and a high salt diet than in normal rats (Champlain, Krakoff & Axelrod 1966; Krakoff, Champlain & Axelrod 1967a, b). Similar results were obtained when hypertension was induced by kidney capsulation followed by contralateral nephrectomy in rats (Volicer, Scheer & others 1968) or by sinoaortic denervation in rabbits (DeQuattro, Maronde & others 1968).

In the course of studies on the antihypertensive effect of α-methyldopa, I observed normal levels of endogenous monoamines in renal hypertensive rats (Henning 1967). Obviously, this finding does not exclude an alteration in the turnover of these amines. Studies of this kind may conveniently be made by means of inhibitors of monoamine synthesis (Andén, Corrodi & Fuxe 1968). It has been found that the reduction of noradrenaline in various tissues after inhibition of tyrosine hydroxylase by α-methyl-*p*-tyrosine methyl ester (H44/68) is largely dependent on the nerve impulse flow (Corrodi & Malmfors 1966; Andén, Corrodi & others 1966). This method has been used in the present investigation to compare the turnover of noradrenaline in various organs of normal and renal hypertensive rats.

The hypertensive rats used in this study were randomly selected from a population of male Sprague-Dawley animals which had been made hypertensive by partial infarction of one kidney in combination with contralateral nephrectomy (Sokabe & Grollman 1963; Henning 1967). Blood pressure was checked in some of the rats by direct recording in the conscious state from a catheter previously implanted in the thoracic aorta (Henning 1967). Nine out of the 22 hypertensive rats used had a mean arterial

Table 1. *Tissue noradrenaline levels in normotensive and renal hypertensive rats normally and after treatment with α-methyl-*p*-tyrosine methyl ester* (H44/68) *as indicated.* The values are means in μg/g tissue and the small figures indicate number of experiments. P values were calculated with analysis of variance; n.s. = not significant

		Brain	Spinal cord	Heart	Femoral muscle	Salivary gland
A.	Normal rats, no treatment	0·502 (5)	0·315 (5)	1·158 (5)	0·090 (5)	1·651 (5)
B.	Normal rats, 4 h after H44/68, 250 mg/kg, i.p.	0·245 (6)	0·188 (6)	1·041 (6)	0·095 (5)	1·075 (6)
C.	Hypertensive rats, no treatment	0·549 (5)	0·309 (5)	1·123 (5)	0·107 (5)	1·728 (5)
D.	Hypertensive rats, 4 h after H44/68, 250 mg/kg, i.p.	0·316 (6)	0·207 (6)	0·730 (6)	0·074 (6)	1·598 (6)
Variance within groups	A–D:	0·0012	0·0013	0·0212	0·0002	0·0441
P value, %;	A–B:	<0·1	<0·1	n.s.	n.s.	<0·1
	A–C:	n.s.	n.s.	n.s.	n.s.	n.s.
	A–D:	<0·1	<0·1	<0·1	n.s.	n.s.
	B–C:	<0·1	<0·1	n.s.	n.s.	<0·1
	B–D:	<0·5	n.s.	<0·5	<2·5	<0·1
	C–D:	<0·1	<0·1	<0·1	<0·5	n.s.

blood pressure of 160 mm Hg (s.e. = 5·5). Normal and hypertensive rats 180–250 g were injected intraperitoneally with H44/68, 250 mg/kg, dissolved in saline. After 4 h, the animals were killed by exsanguination under light chloroform anaesthesia. Brain, spinal cord, heart, left submaxillary gland and femoral muscle were dissected and analysed for noradrenaline (Bertler, Carlsson & Rosengren 1958). The organs from two animals were pooled. Analysis of variance (Davies 1949), with P values equal to or less than 0·025 were regarded as significant.

The noradrenaline content of the brain and the spinal cord was the same in normal and hypertensive rats and was lowered to about the same extent by treatment with H44/68 (Table 1). Heart and femoral muscle noradrenaline levels were also the same in untreated animals from the two groups. However, in both heart and muscle, H44/68 lowered noradrenaline significantly more in hypertensive rats than in normal animals. Salivary glands were depleted significantly in normal rats but not in hypertensive animals; the difference between the two groups was statistically significant.

If the lowering of noradrenaline after tyrosine hydroxylase inhibition mainly depends on nerve impulse flow (Corrodi & Malmfors 1966; Andén & others 1966; Andén, Corrodi & Fuxe 1968), the present results indicate that renal hypertension in rats is associated with an increased impulse flow in the sympathetic nerves to the heart and femoral muscle, when compared to normal animals. By the same reasoning, a decreased sympathetic activity may exist in the case of the salivary glands. In our experiments, the basal levels of endogenous noradrenaline were the same in normal and hypertensive animals. This is in contrast to the observations by Champlain & others (1966) and Krakoff & others (1967a, b) but in agreement with those of Volicer & others (1968) who used rats with a type of hypertension similar to that induced in the present experiments. The changes in the storage and release of noradrenaline found by the above-mentioned investigators may be interpreted in terms of an increased impulse flow in the sympathetic nerves. On the other hand, the results of the present study do not exclude an alteration in the transmission mechanisms in these nerves, as suggested by these authors. Further, there may be differences between various types of experimental hypertension.

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REFERENCES

ANDÉN, N.-E., CORRODI, H., DAHLSTRÖM, A., FUXE, K. & HÖKFELT, T. (1966). *Life Sci.*, **5**, 561–568.

ANDÉN, N.-E., CORRODI, H. & FUXE, K. (1968). *Br. J. Pharmac.*, in the press.

BERTLER, Å., CARLSSON, A. & ROSENGREN, E. (1958). *Acta physiol. scand.*, **44**, 273–292.

CHAMPLAIN, J. DE, KRAKOFF, L. R. & AXELROD, J. (1966). *Life Sci.*, **5**, 2283–2291.

CORRODI, H. & MALMFORS, T. (1966). *Acta physiol. scand.*, **67**, 352–357.

DAVIES, O. L. (1949). *Statistical methods in research and production*, London: Oliver & Boyd.

DEQUATTRO, V., MARONDE, R., NAGATSU, T. & ALEXANDER, N. (1968). *Fedn Proc. Fedn Am. Socs exp. Biol.*, **27**, 240.

HENNING, M. (1967). *J. Pharm. Pharmac.*, **19**, 775–779.

KRAKOFF L., CHAMPLAIN, J. DE & AXELROD, J. (1967a). *Fedn Proc. Fedn Am. Socs exp. Biol.*, **27**, 682.

KRAKOFF, L. R., CHAMPLAIN, J. DE & AXELROD, J. (1967b). *Circulation Res.*, **21**, 583–591.

SOKABE, H. & GROLLMAN, A. (1963). *Tex. Rep. Biol. Med.*, **21**, 93–100.

VOLICER, L., SCHEER, E., HILSE, H. & VISWESWARAM, D. (1968). *Life Sci.*, **7**, 525–532.

Enhancement of the convulsant action of thiosemicarbazide in mice

Reserpine-like agents enhance seizure suceptability to leptazol (Chen, Ensor & Bohner, 1954) and reduce the effectiveness of most, if not all, anticonvulsants in mice (Chen & others, 1954; Gray, Rauh & others, 1958, 1963; Mennear & Rudzik, 1966). I have now made experiments on the effects of two catecholamine-depleting agents on the convulsant activity of thiosemicarbazide.

Male albino mice (Harlan Industries), 18–22 g, were housed in groups of 25 before experimentation and then individually after intraperitoneal injection of 100 mg/kg of thiosemicarbazide. Ten mice were used in each experimental group.

α-Methyltyrosine, suspended in corn oil, was administered intraperitoneally in three daily doses of 150 mg/kg. Ninety min after the administration of the third dose the mice received an intraperitoneal injection of thiosemicarbazide. The second catecholamine depletor, Ro4-1284 (2-ethyl-1,2,3,4,6,7-hexahydro-2-hydroxy-3-isobutyl-9,10-dimethoxy-11b*H*-benzoquinolizine), was administered in an intraperitoneal dose of 20 mg/kg simultaneously with the dose of thiosemicarbazide. Three end points were measured; the onset time for clonic seizures; the onset time for tonic seizures and the time of death.

The results summarized in Table 1 show the potentiating effect of Ro4-1284 on the convulsant action of thiosemicarbazide. In control mice the mean latency time for the onset of the initial clonic seizure was 41 ± 4 min and tonic seizures developed

Table 1. *Effect of* Ro4-1284* *and α-methyltyrosine‡ (α-MT) on the convulsant action of thiosemicarbazide†*

	Ro4-1284*			α-Methyltyrosine		
End point	Treatment	Min to end point ± s.e.	P	Treatment	Min to end point ± s.e.	P
Clonic seizure	Control	41 ± 4	<0·05	Control	31 ± 2	n.s.
	Ro4-1284	30 ± 2		α-MT	36 ± 4	
Tonic seizure	Control	46 ± 4	<0·01	Control	36 ± 2	n.s.
	Ro4-1284	30 ± 2		α-MT	36 ± 4	
Death	Control	54 ± 2	<0·001	Control	49 ± 3	<0·05
	Ro4-1284	30 ± 2		α-MT	37 ± 4	

* 20 mg/kg i.p. † 100 mg/kg i.p. ‡ 150 mg/kg/day for 3 days.