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Effects of Drugs and Physiological Factors in the Disposition of Catecholamines in Blood Vessels

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THE systemic arterial blood pressure is the resultant of the peripheral hemodynamic resistance and the function of the heart. The vascular bed, which exerts a distinct role in the maintenance of circulatory homeostasis is innervated by postganglionic adrenergic fibers. The biological assay (4) determinations confirmed by histochemical fluorescent studies (9, 11, 23) afforded early evidence that the sympathetic nerve terminations around the blood vessels contain norepinephrine.

Our concepts in regard to the regulation of the adrenergic transmitter substance as it effects synthesis, storage, uptake and metabolism have been derived mainly by those investigators who have studied many well defined adrenergically innervated neuroeffectors such as the heart and spleen. However, too little has been done to define the control of the norepinephrine released at the blood vessels.

Many adrenergically innervated tissues have the capability of reabsorbing into the adrenergic neurons the released adrenergic neurotransmitter. Maxwell *et al.* (21), and Nedergaard and Bevan (22) and de la Lande (19) are among many who have shown that arteries possess an uptake mechanism. The question then arises as to whether the endogenous content of the amine in the vasculature is a consequence of this re-uptake mechanism or whether the enzymatic machinery is of primary importance. This question can best be studied by investigating the biosynthesis and catabolism of the transmitter in the blood vessels.

It is apparent after examination of the vascular tissue from three species, namely rat, guinea pig and rabbit (table 1), that the blood vessels contain appreciable levels of norepinephrine. The endogenous content in general is equal to or greater than cardiac norepinephrine content. Of particular interest was the high endogenous content seen in the mesenteric vasculature. Anatomical studies with histofluorescent techniques have established the dense adrenergic innervation of this bed. Our studies chemically confirm the high norepinephrine content but also indicate that the distal mesenteric artery and branches contain more than twice that noted in the proximal portion (table 2). This is true not only for the rat, but also for the rabbit. The thoracic aorta, which is usually used as the model tissue for studying the pharmacology of the vasculature has levels that are roughly $\frac{1}{10}$ that of the mesenteric artery. Genest *et al.* (12) used dog mesenteric arteries and has reported similar findings in regard to the high endogenous norepinephrine concentrations.

TABLE 1

Concentration of norepinephrine in the heart, arteries and veins of rat, rabbit and guinea pig

Species*	Tissue Norepinephrine (μg/g)†					
	Aorta‡	Mesenteric artery‡	Renal artery‡	Heart‡	Vena cava‡	Mesenteric vein‡
Rat	0.44 ± 0.05 (17)	2.76 ± 0.34 (13)	2.09 ± 0.85 (5)	1.01 ± 0.04 (17)	1.84 ± 0.32 (5)	2.67 ± 0.57 (8)
Guinea pig	1.37 ± 0.16 (10)	2.89 ± 0.47 (10)	5.8 (1)	1.43 ± 0.11 (10)	2.82 (2)	2.04 ± 0.21 (4)
Rabbit	1.98 ± 0.52 (9)	2.67 ± 0.39 (7)	3.70 ± 0.61 (4)	1.08 ± 0.09 (7)	3.26 ± 0.65 (7)	1.54 ± 0.19 (4)

* Rats were 200 g females; guinea pigs were 200 to 400 g males, and rabbits were 2 Kg males.

† Results are the mean ± S.E. and are corrected for recovery loss. The numbers in parentheses indicate the number of experiments.

‡ Vessels were pooled for each experiment: Rat, 5–7 aortas; 3–5 mesenteric arteries; 5 vena cavas, renal arteries and mesenteric veins. Guinea pig, 3–5 aortas; 3–5 mesenteric arteries; 5 vena cavas and mesenteric veins. Rabbit individual aortas, 1–2 mesenteric arteries, 2–3 vena cavas, mesenteric veins and renal arteries. Hearts were analyzed individually and the results from at least 5 rats or guinea pigs and 2 to 3 rabbits per experiment were averaged.

TABLE 2

Regional distribution of norepinephrine in aorta and mesenteric artery of the rat and rabbit

Tissue*	Norepinephrine (μg/g)†	
	Rat	Rabbit
Aorta		
Thoracic	0.10 (0.09–0.11)	0.26 (0.25–0.27)
Abdominal	0.43 (0.36–0.50)	1.50 (1.25–1.74)
Mesenteric artery		
Proximal	1.74 (1.33–2.16)	2.04 (2.04)
Distal	4.64 (3.23–6.06)	4.62 (4.2–5.1)

* The aorta was divided at the diaphragm into thoracic and abdominal portions.

† The results are the average of two experiments and the numbers in parentheses indicate the range. Tissue from 14 rats and 5 rabbits were analyzed.

It is also recognized that veins are sympathetically innervated and are responsive to sympathetic stimulation (7). Histofluorescent studies indicate that the density of innervation although appreciable is significantly less than in the arterial bed (23); however, veins contain so little muscle tissue that when content is expressed as μg/g of tissue the levels are at least 50 % of the corresponding arteries. Relatively little has been done on the regulation of catecholamines in veins. Rolewicz and Zimmerman (24) Rolewicz *et al.* (25) have pointed out that veins possess a more efficient re-uptake mechanism than arteries. It is of interest that we found that 6-hydroxydopamine, which must be taken up by the adrenergic neuron to effect chemical sympathectomy, is a more effective depletor of norepinephrine in veins than arteries (table 7). It cannot be assumed that the disposition of norepinephrine or the effects of drugs on veins will be identical to other areas of the

cardiovascular system or other adrenergically innervated tissues and so this is a tissue that merits further investigation.

The role that the re-uptake process plays in the physiological disposition and conservation of norepinephrine in the heart is well recognized and accepted. As to whether this process plays as vital a role in the vascular disposition of norepinephrine has not been established. Su and Bevan (30) have suggested from studies *in vitro* that almost all of the norepinephrine released from the pulmonary artery can be "recaptured" by the tissue. However, the studies of de la Lande *et al.* (19) have shown that drugs are much more effective in blocking re-uptake of norepinephrine when applied on the outside of the vessel than from the lumen. With respect to the physiological consequences of blocking the re-uptake system response, cocaine potentiation of norepinephrine is much more pronounced in cardiac tissue than vascular tissue (14). Furthermore, Shibata *et al.* (27) and Kalsner and Nickerson (15–17) reported that cocaine-induced potentiation of norepinephrine effects on the aorta may not be related to an action on the adrenergic nerve terminals. The simplest and yet best evidence arguing against a major re-uptake component of released norepinephrine normally is the relatively large distance between nerve endings and muscle effectors in blood vessels (32).

Our studies have shown that the uptake *in vivo* of circulating norepinephrine into blood vessels is much less than into the heart; in fact, vessels may take up as little as ¼ to 1/15 that of the heart (fig. 1). Figure 2 shows that administration of cocaine or desmethylimipramine (DMI), two agents which block neuronal

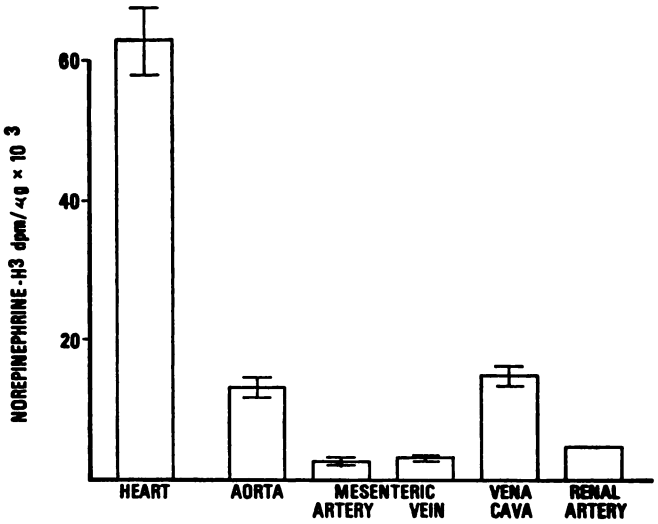

FIG. 1. Uptake of norepinephrine-^{3}H by blood vessels and heart in the rat. Three microcuries of tritiated norepinephrine (5 Ci mmol) were injected intravenously and the rats were sacrificed 10 min later and specific activity determined. Results from 10 hearts were averaged and three groups of pooled vessels (five vessels per group) with the exception of the renal artery for which two groups were averaged (seven vessels per group). Vertical bars indicate the S.E.

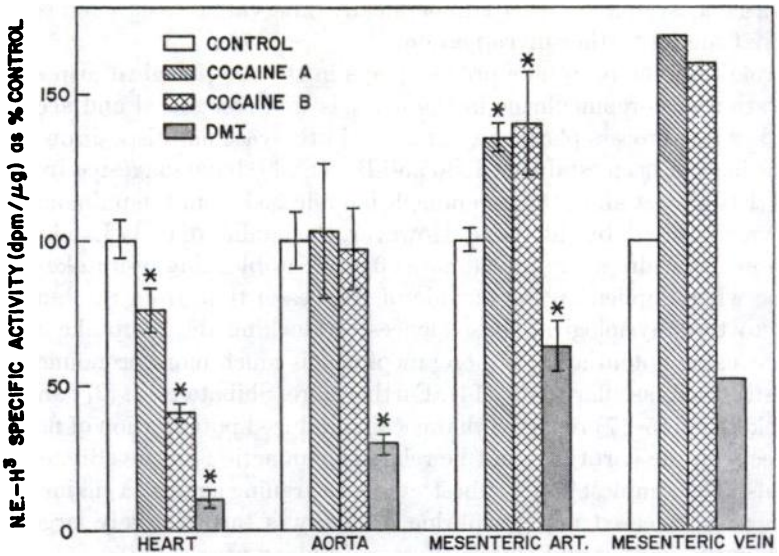

FIG. 2. Influence of cocaine and desmethylimipramine on the uptake of norepinephrine-^{3}H by the heart and vascular system of the rat. Control rats received 3 μc of L-norepinephrine-^{3}H intravenously and were sacrificed 10 min later. Cocaine A and B were pretreated with 10 mg/kg cocaine intraperitoneally 60 and 10 min respectively before norepinephrine-^{3}H and desmethylimipramine was administered intraperitoneally 10 mg/kg 30 min prior to norepinephrine-^{3}H. Results from five hearts or three groups of vessels were averaged and expressed as percent controls ± S.D. with the exception that two groups of mesenteric veins were averaged. Specific activities of controls were heart 60,000, aorta 13,000, mesenteric artery 2700 dpm/μg, and mesenteric vein 2700 dpm/μg. *Statistically significant $P < .05$.

uptake of norepinephrine into the heart, were either not effective at all, as seen in instance of cocaine, or only partially effective as is the case with DMI.

Thus our data do not support neuronal uptake and re-uptake as the dominant factor regulating norepinephrine disposition in blood vessels. However, we feel that one should not neglect the possibility that the re-uptake process may be variable; during certain physiological and pathological states this process may be altered. If neuronal uptake or re-uptake of norepinephrine is of secondary importance, an alternate explanation must be offered to account for the physiological disposition and termination of action of the amine as well as for the mechanism which serves to maintain and to conserve norepinephrine content.

We feel that an enzymatic component in blood vessels is a major factor not only in the maintenance of functional levels of the neural transmitter but in regulating its disposition. Studies were carried out to ascertain whether the high levels of norepinephrine in the vasculature would be reflected in the activity of tyrosine hydroxylase, the rate limiting step in norepinephrine biosynthesis. Table 3 shows that tyrosine hydroxylase activity in the blood vessels is 2- to 10-fold greater than cardiac tissue and that the mesenteric artery has an activity comparable to that of the adrenal gland. The tyrosine hydroxylase activity is consistently greater in the mesenteric artery when compared to the heart not only for the rat

TABLE 3

Tyrosine hydroxylase activity in various tissues

Tissue	Tyrosine Hydroxylase*	
	cpm/mg Protein/hr†	nmol dopa/mg Protein/hr
Heart (12)	828 ± 100	0.10 ± 0.01
Mesenteric artery (8)	9968 ± 2328	1.32 ± 0.40
Mesenteric vein (8)		2.33 ± 0.33
Aorta (8)	1728 ± 544	0.22 ± 0.36
Adrenal (8)		3.80 ± 0.36

* In the determination of tyrosine hydroxylase in the vessels, two samples were pooled and homogenized (30 mg of blood vessels in 0.1 ml of water). Hearts were passed through a Baruch tissue press. Homogenates and pressed tissue were centrifuged (30,000 × *g* for 20 min.) and the supernatant was incubated with 0.12 μmol dimethyltetrahydropteridine ($DMPH_4$), 120 μmol mercaptoethanol, 100 μmol sodium acetate buffer (pH 6.0) and 0.05 μmol ^{3}H-tyrosine (4×10^6 dpm.). Incubation was for 15 min at 37°C and terminated by addition of 0.5 ml of 5% trichloroacetic acid. Supernatant of incubation mixture was passed over a Dowex 50 H^+ column and tritiated water was collected and counted. Figures represent mean ± S.D. of 18 experiments.

† In addition to the above incubation medium, flasks with heart, aorta and mesenteric artery contained 20 nmol of non-radioactive tyrosine and those flasks with adrenal gland contained 50 nmol tyrosine.

TABLE 4

Monoamine oxidase activity in cardiovascular tissue

Tissue	Rat	Guinea Pig	Rabbit
	mμ moles 5 HIAA/mg protein/25 min*		
Heart	4.91 ± 0.46 (8)†	3.74 ± 0.47 (8)†	0.10 ± 0.02 (2)†
Mesenteric artery	3.31 ± 0.51 (6)†	12.7 ± 2.3 (8)†	0.72 ± 0.07 (2)†
Aorta	1.87 ± 0.56 (6)†	2.59 ± 0.23 (6)†	0.21 ± 0.07 (2)†

* 5-HIAA, 5-hydroxyindoleacetic acid.

† Figures represent mean ± SD. The numbers in parentheses indicate the number of determinations.

but also the guinea pig and rabbit (29). The low activity in the heart is a consistent finding by many groups and remains unexplained.

Only recently has attention been given to the role of catecholamine degradative enzymes in the vasculature (17). Table 4 shows that the enzymes monoamine oxidase and catechol-O-methyl transferase exhibit appreciable activity in the vasculature. The guinea pig and rabbit show a greater activity of monoamine oxidase in the mesenteric artery than in the heart, whereas in the rat the activity of the enzyme is almost the same in both tissues. In regard to catechol-O-methyl transferase activity the vasculature had an activity equal to that of the heart (table 5). The marked activity of catechol-O-methyl transferase in the vasculature provides biochemical support for the studies of Kalsner and Nickenson (17) who

TABLE 5

Catechol-O-methyl transferase activity in heart and blood vessels

Tissue*	Rat	Rabbit
	cpm × 10^4/*hr*/*mg protein*	
Heart	5.69 ± 0.70 (22)	10.31 ± 1.9 (4)
Mesenteric artery	14.2 ± 3.8 (32)	15.58 ± 3.0 (14)
Mesenteric vein	24.66 ± 3.6 (5)	7.2 ± 1.7 (3)
Aorta	11.84 ± 3.7 (19)	

* Tissues were homogenized in 4 volumes of 1.15 M KCl and centrifuged (30,000 × *g*, 40 min). The supernatant was incubated for 12 min with 200 mμmol of S-adenosyl methionine, 250 mμmol of $MgCl_2$, 150 mμmol of 3,4-dihydroxypropiophenone, 10 μmol of K-phosphate buffer, pH 8.0, and 0.5 mμmol of ^{14}C S-adenosyl methionine (5.5 × 10^4 dpm). Reaction was terminated with 1 N HCl, and the labeled product was extracted into toluene and counted. Figures represent mean ± S.D. The numbers in the parentheses indicate the number of determinations.

TABLE 6

Turnover of norepinephrine in the blood vessels and heart of the rat

Tissue*	Half-life†	*k* NE*	Synthesis Rate‡
	hr	hr^{-1}	*μ/g/hr*
Norepinephrine-^3H			
Heart (4)	10.6 ± 0.78	0.07 ± 0.01	0.07 ± 0.00
Aorta (4)	10.5 ± 2.03	0.09 ± 0.01	0.04 ± 0.01§
Mesenteric artery (4)	10.2 ± 2.40	0.07 ± 0.02	0.15 ± 0.03§
α-MPT‖			
Heart (5)	11.9 ± 1.0	0.063 ± 0.02	0.07 ± 0.02
Aorta (1)	8.0	0.087	0.053
Mesenteric artery (2)	12.7 (12.3, 13.1)	0.054	0.25
Mesenteric vein (1)	10.2	0.068	0.31

* Norepinephrine-^3H, 10 μc, was administered intravenously and the rats were killed at regular intervals up to 30 hr. Decay of norepinephrine specific activity was plotted for each experiment and *k* NE (rate constant) was calculated by fitting the data by method of least squares [Brodie *et al.* (3a)]. At least four determinations were made for each heart and one to four for each vessel for each time interval. The numbers in parentheses indicate the number of experiments averaged ± S.E.M. Single values represent the data from one or the average of two experiments.

† Individual half-lives were obtained by using the equation $T1/2 = 0.693/k$ NE. Half-lives shown are the average ±S.E.M. for the number of experiments.

‡ A synthesis rate was calculated by multiplying *k* NE times the concentration of norepinephrine at the beginning of the experiment.

‖ α-Methyl tyrosine methyl ester (α-MPT) was administered intravenously (200 mg/kg, slowly) and rats were killed at regular intervals up to 8 hr. Kinetic calculations were based on the decay of endogenous norepinephrine [Spector *et al.* (28a)].

§ Statistically significant $P < .05$.

showed that enzymatic degradation rather than neuronal re-uptake and storage disposes of the bulk of the physiologically active catecholamine in blood vessels.

Considering the great expanse of the vasculature and its appreciable sympathetic innervation (1, 2, 26, 28), it could be a source of a major fraction of both

circulating and excreted norepinephrine. However, information is lacking on the kinetics of norepinephrine synthesis in blood vessels *in vivo* although a number of investigators have studied its disposition in the heart and certain vascular beds (13, 18).

Studies on the synthesis of norepinephrine are seen in table 6. Based on the decline of the specific activity of tissue norepinephrine after an intravenous pulse of norepinephrine-^{3}H, the half-life of norepinephrine was found to average between 9 and 11 hr in the rat heart, aorta, or mesenteric artery. A similar half-life of 8 to 12 hr was estimated by determining the decline of norepinephrine content after inhibition of tyrosine hydroxylase with α-methyltyrosine. For the mesenteric artery, our estimate of half-life may be conservative since administration of a monoamine oxidase inhibitor doubled the concentration of norepinephrine in this bed within 5 hr (2).

Although these data show roughly similar half-lives for vascular and cardiac tissue, the synthesis rates in the mesenteric artery and vein were quite different from the heart. Synthesis in the mesenteric artery and vein was 0.15 to 0.3 μg/g/hr, a rate at least twice that of the heart.

In two experiments in the rabbit we have measured a norepinephrine synthesis rate of 0.6 μg/g/hr in the mesenteric artery and vein. This observation *in vivo* is in agreement with the recent study of Gillis and Roth (13), who reported a rapid

TABLE 7

Effect of 6-hydroxydopamine (6-OHD) on the concentration of catecholamines in the rat and guinea pig

Species and Tissue	Noradrenaline (μg/g)*		
	Control	6-OHD	Decrease after 6-OHD
			%
Rat			
Heart	1.13 ± 0.13	0.15 ± 0.02†	87
Aorta	0.41 ± 0.23	0.16 ± 0.02	61
Mesenteric artery	3.39 ± 0.75	2.43 ± 0.43	28
Mesenteric vein	2.30 ± 0.04	0.50 − 0.70	75
Spleen	0.30 ± 0.04	0.05 ± 0.01†	83
Adrenal glands	22.60 ± 0.74	24.90 ± 0.79	0
Guinea pig			
Heart	1.59 ± 0.13	0.07 ± 0.03†	96
Aorta	2.50 ± 0.64	1.08 ± 0.58	57
Mesenteric artery	2.27 ± 0.09	1.12 ± 0.15†	51
Mesenteric vein	0.79 ± 1.00	0.13 − 0.33	84

* The results are the mean of 5 to 6 determinations ± S.E.M. for heart, spleen and adrenal catecholamines. Vessels were pooled: 4 aortas, 3 mesenteric arteries and 5 mesenteric veins for each determination and three determinations averaged except for the mesenteric vein where the range of two determinations is given. 6-OHD was administered to rats (140 g intravenously) twice within 24 hr on day 1, 50 mg/kg twice on day 7, 100 mg/kg. The rats were killed on day 15. 6-OHD (50 mg/kg intraperitoneally) was injected into guinea pigs and sacrificed 24 hr later. Adrenal noradrenaline is as μg/pair of adrenal glands.

† The difference between controls and treated animals statistically significant $P < .05$.

synthesis of catecholamines in rabbit arteries and veins studied *in vitro* (0.1–0.6 μg/g/hr).

We propose that the vasculature because of its expanse and rapid rate of norepinephrine synthesis may be the source of a large, perhaps the major, fraction of excreted catecholamines. Other evidence supports this. Bigelow *et al.* (3) have indicated that most of the excreted catecholamines arise from sites other than

TABLE 8

Effect of immunosympathectomy on catecholamines in the heart and blood vessels of the rat

Tissue	Noradrenaline (μg/g)*		
	Control	Immunosympathectomy	Change
			%
Heart	1.00 ± 0.06	0.30 ± 0.13†	70
Aorta	0.64 ± 0.10	0.33 ± 0.03	48
Mesenteric artery	4.20 ± 0.24	2.00 ± 0.05†	52
Mesenteric vein	(1.94 − 2.58)	(1.28 − 1.35)	42

* Double strength horse nerve growth factor antiserum was injected subcutaneously on 5 consecutive days beginning on the day of birth. Rats were killed when they weighed 200 g. Five hearts, three groups of aortas or mesenteric arteries and two groups of mesenteric veins were assayed and the results expressed as mean ± S.E.M. Tissues pooled as in table 1.

† Statistically significant as compared to control animals ($P < .05$).

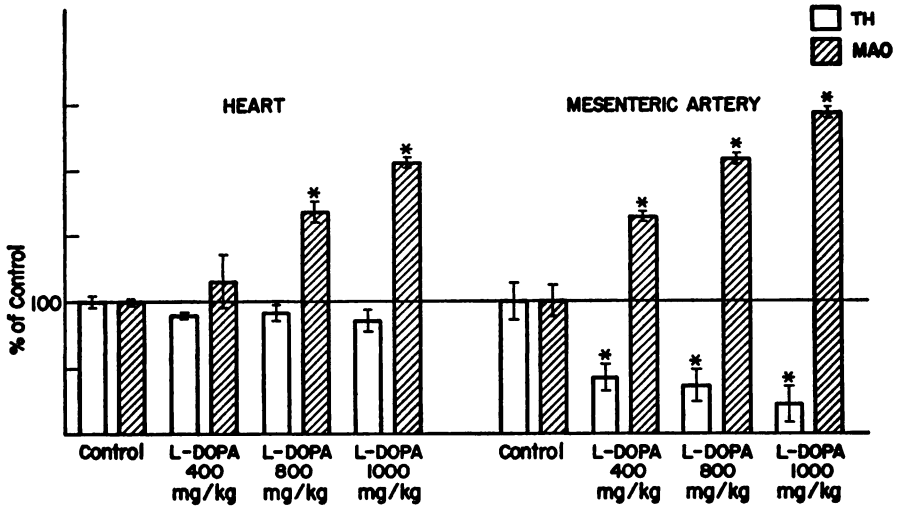

FIG. 3. Effect of L-dopa (5 days) on tyrosine hydroxylase (TH) and monoamine oxidase (MAO) activity. L-Dopa was homogenized in saline and injected as a suspension subcutaneously once per day for 5 days. Animals were killed 24 hr after the last dose. TH determinations were performed on a pool of two tissues and MAO activity on single tissues. Vertical bars indicate S.D. N = 14. *$P < .05$ or greater.

heart, adrenal, brain, spleen or submaxillary glands. For man, Maas and Landis (20) have found that most of the endogenous urinary norepinephrine metabolites originate in pools which, related to their total rates of norepinephrine synthesis or size, are penetrated poorly or not at all by circulating norepinephrine. It is noteworthy, therefore, that blood vessels take up circulating norepinephrine relatively poorly, extracting ¼ to 1/15 as much amine as the rat heart (2). Further evidence is that immunosympathectomy (5, 6) only partially reduces urinary excretion of norepinephrine and metabolites. This finding may be explained by the fact that the mesenteric artery and other vascular beds are much more resistant to norepinephrine depletion by immunosympathectomy or chemical sympathectomy than are the heart and other peripheral organs (tables 7 and 8).

If the above arguments are valid, a significant fraction of circulating norepinephrine and any enzymes or granular contents released along with it are also of vascular origin. In this regard, at least 60% of circulating dopamine-β-hydroxylase may be derived from blood vessels (33).

The studies with 6-hydroxydopamine and immunosympathectomy showing only partial reduction of vascular catecholamines raises an important point: namely, drugs which are known to influence catecholamine content in the heart need not exhibit a comparable effect on the vasculature. Thus, the reason for the resistance of experimental hypertension to either 6-hydroxydopamine or anti-nerve growth factor as noted by Varma (31), and by Finch and Leach (10), could be explained by the presence of sufficient norepinephrine in critical sites in the blood vessels to maintain peripheral resistance.

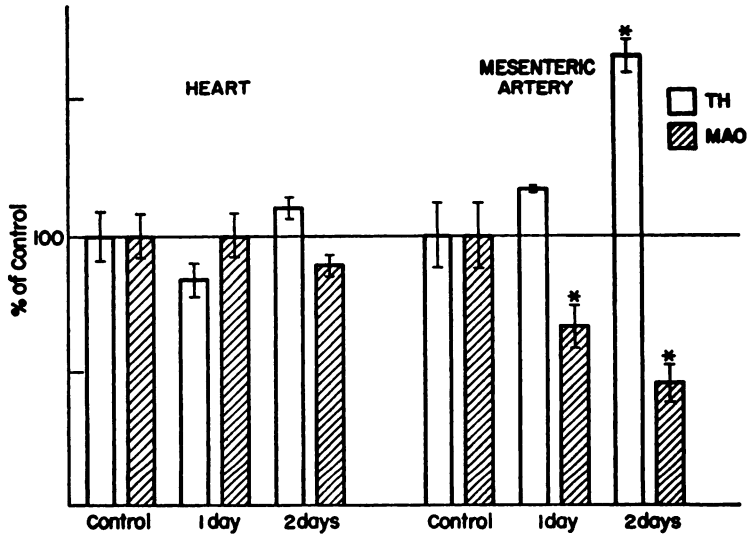

FIG. 4. Effect of reserpine 1.5 mg/kg on tyrosine (TH) and monoamine oxidase activity. Reserpine (1.5 mg/kg) was administered intraperitoneally as a single dose for 1 or 2 days and the animals killed 24 hr later. TH determinations were performed on a pool of two tissues. Activity of MAO was determined on single tissues. Vertical bars indicate the S.D. N = 12. *P < .05 or greater.

A great emphasis on the regulation of catecholamines has been directed to those enzymes which are involved in its biosynthesis. However, consideration also should be made with regard to the influence that alterations in activity of degradative enzymes might exert in consort with changes in synthetic enzymes. Figure 3 shows that the administration of large doses of L-dopa causes a decrease in tyrosine hydroxylase activity in blood vessels, although not the heart. While many studies have shown tyrosine hydroxylase to be an inducible enzyme, our data suggests that the activity can also be diminished. The ability to decrease tyrosine hydroxylase activity is not restricted to the vasculature as Dairman and Udenfriend (8) have also reported a decrease in adrenal tyrosine hydroxylase after L-dopa administration. Of particular interest was that concomitant with this decrease in vascular tyrosine hydroxylase activity there is a dose-dependent increase in monoamine oxidase activity. Figure 4 also shows that reserpine which elicited no change in activity of either enzyme in the heart, caused an increase in tyrosine hydroxylase activity while at the same time reducing monoamine oxidase activity in the mesenteric artery. Thus, one notes a reciprocal regulation that may be operative. This interaction may be operative not only after drug treatment, but also during certain pathophysiological states. The physiological stimulus for these changes after reserpine may well be a consequence of the hypotension, as the blood pressure falls by 30 mm Hg.

The spontaneously hypertensive rats afforded us the opportunity to look at the opposite situation, namely the effect that hypertension may manifest on these enzymes. Table 9 shows that cardiac tyrosine hydroxylase activity was unaltered; however, the activity in the mesenteric artery was markedly reduced. Preliminary evidence indicates that both monoamine oxidase and catechol-O-methyl transferase are elevated. It would appear that vascular homeostasis may be maintained by alteration in activity of both the synthetic and degradative enzymes.

TABLE 9

Tyrosine hydroxylase activity in the spontaneously hypertensive rat (SHR)

Animal	Blood Pressure Range	Tissue	Tyrosine Hydroxylase Control
	mm Hg		%
Wistar	110–120	Heart (3)*	100 ± 16
Wistar × SHR†	120–150	Heart (3)	125 ± 12
SHR	160–180	Heart (6)	100 ± 16
Wistar	110–120	Mesenteric artery (3)	100 ± 16
Wistar × SHR†	120–150	Mesenteric artery (3)	65 ± 21
SHR	160–180	Mesenteric artery (3)	32 ± 10‡

* The numbers in parentheses indicate the number of determinations. Tissues from two animals were pooled for each determination. Figures represent mean ±S.D.

† Backcrossed SHR.

‡ $P < .001$.

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