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Research Article

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THE PRESSOR EFFECT OF TYRAMINE IN MAN AND ITS MODIFICATION BY RESERPINE PRETREATMENT *

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Reserpine has been shown to cause depletion of catecholamines in various isolated tissues and in pharmacological preparations of intact animals (1–5). Several aspects of the alterations in body function associated with administration of reserpine to man have been reported: in two schizophrenics who had received reserpine, de la Lande and associates (6) showed that ephedrine infused into the brachial artery had no effect on forearm blood flow; Westfall and Watts (7) showed that in normal students there was a diminished response of blood pressure and finger temperature to smoking after fourteen days of reserpine administration; Burger (8) found diminished plasma norepinephrine levels, and Gaddum, Krivoy, and Laverty (9) and Carlsson, Rasmussen, and Kristjansen (10) described decreased urinary excretion of catecholamines after long term reserpine administration. However, there appear to be no formal studies in man showing that reserpine affects cardiovascular responses, as has been postulated to explain the circulatory collapse which may occur in patients who have received reserpine and are subjected to anesthesia (11) and shock therapy (12). Depletion of the tissue stores of norepinephrine should result in a reduced pressor effect of tyramine, as this is believed to be due entirely to release of endogenous norepinephrine (13–14). The modification of the cardiovascular response to tyramine by pretreatment with moderate doses of reserpine is reported here.

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MATERIAL AND METHODS

Twelve male patients aged 37 to 73 were studied (Table I). They had all been in-patients for a considerable time and were free of obvious cardiovascular disease, ascites, and peripheral neuropathy. They were not receiving reserpine, sympathomimetic amines, or monamine oxidase inhibitors.

The subject lay comfortably on a couch, and polyethylene catheters were placed in the brachial artery on one side and a forearm vein on the other. Blood pressure was recorded continuously with a Sanborn capacitance manometer model no. 267B or a Statham resistance manometer model no. 23B4 and a Sanborn recorder model no. 150M. In some studies, the blood pressure was electrically meaned, in others an instantaneous recording was obtained and mean arterial pressure (MAP) estimated by the formula MAP = diastolic blood pressure plus ⅓ pulse pressure. Cardiac outputs (CO) were estimated by dye dilution with indocyanine green, a Colson cuvette densitometer model no. 110 I.R., and Harvard pump model 600–900. Duplicate determinations of CO before injections of tyramine gave 95% confidence limits for the method of ± 0.64 L per mm. Total peripheral resistance (TPR) was calculated from the formula TPR (dyne-sec-cm^{-5}) = 80 × MAP (mm Hg)/CO (L per minute).

Each subject was studied on two occasions 48 hours apart. On day 1, after the catheters were satisfactorily

TABLE I

Patient material

Patient	Age	Diagnosis	Reserpine-treated or control
	yrs		
1	54	Laennec's cirrhosis	R
2	73	No organic disease	R
3	54	Convalescent from diarrhoea	R
4	37	Korsakoff's psychosis	R
5	60	Carcinoma of larynx	R
6	51	Multiple sclerosis	C, R*
7	43	Healed duodenal ulcer	C
8	69	Cerebral thrombosis	C
9	53	Cervical spondylosis	C
10	50	Laennec's cirrhosis	C
11	50	Laennec's cirrhosis	R
12	40	Treated hypothroidism	R
Mean	52.8		

* See text.

TABLE II

*Effects of tyramine**

Subject	Pulse rate		MAP		MAP curve area	CO		TPR	
	Initial	Maximal change	Initial	Peak rise		Initial	Change 1½ min after tyramine	Initial	Change 1½ min after tyramine
	beats/min		*mm Hg*		*mm-min*	*L/min*		*dyne-sec-cm⁻⁵*	
1	84	−20	70	62	270	3.24	−0.60	1,703	+1,475
2	80	−12	85	25	80	4.05	+0.10	1,526	+ 679
3	85	+16	85	67	217	4.74	+0.09	1,397	+1,098
4			87	22	62	5.14	−1.01	1,482	+ 652
5			100	43	224	5.10	−2.19	1,569	+2,426
6	95	+25, −15	112	37	60	4.29	+0.31	2,090	+ 262
7	68	−22	76	61	177	2.99	−0.64	2,103	+2,145
8	64	+20	89	30	50	3.73	+1.18	1,852	+ 19
9	75	−27	89	35	153	4.97	+1.56	1,323	− 37
10	88	−25	100	52	198	5.05	+0.82	1,586	+ 281
11	72	+26	107	80	254	5.19	−0.12	1,780	+ 636
12			92	35	75				
Mean				45.7	152		−0.05		+ 876
SD				18.4	82.3		1.06		828

* Abbreviations: MAP = mean arterial pressure; CO = cardiac output; TPR = total peripheral resistance.

placed and the blood pressure had stabilized, two dye curves were obtained. Tyramine, 0.2 mg per kg (Figure 1), was given intravenously and the blood pressure record continued for at least ten minutes. Further dye curves were obtained at 1½, 5, and 10 minutes after injection. The observations made before and after tyramine on day 1 were repeated on the second occasion. At the conclusion of observations on day 1, eight of the subjects received reserpine, 0.03 mg per kg, intravenously and again 24 hours later, so that by the time these eight subjects were restudied, 48 hours after the first observations, 0.06 mg per kg of reserpine had been given. One subject was studied on three occasions at 48-hour intervals, receiving reserpine between the second and third studies; thus he appears in both control and treated groups. In two of the control subjects, two injections of tyramine were given on each study day and thus yielded two sets of measurements for certain of the comparisons.

RESULTS

I. Control studies of tyramine

Injection of tyramine in this dose produced few side effects. At the height of the blood pressure rise, some subjects experienced throbbing headache and a sense of constriction in the neck.

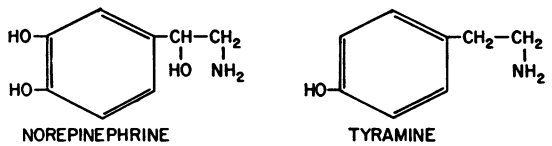

FIG. 1. STRUCTURE OF NOREPINEPHRINE AND TYRAMINE.

The responses of all 12 subjects to the first injection of tyramine are listed in Table II.

Pulse rate. Data on pulse rate after tyramine are available in nine subjects. In four there was a rise of 16 to 27 beats per minute (average, 22 beats per minute) which reached a peak in 1 to 2 minutes; in one of these subjects there was a subsequent fall. In five subjects there was a fall in pulse rate of 12 to 27 beats per minute (average, 21 beats per minute) reaching a nadir at 3 minutes. Pulse rate had usually returned to preinjection level within 5 minutes.

Blood pressure. MAP rose in all subjects owing to a rise in both systolic and diastolic pressures, the absolute increase in the former being about three times the latter. Peak increment of MAP averaged 45.7 mm Hg and occurred at from 1 to

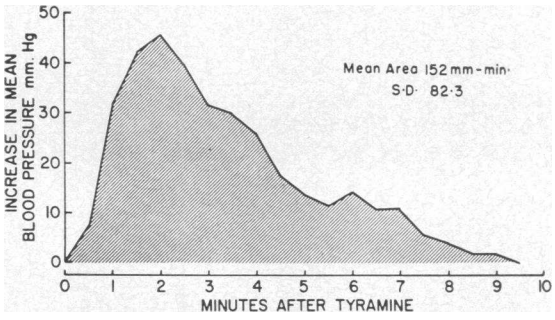

FIG. 2. AVERAGE RESPONSE OF MEAN ARTERIAL PRESSURE TO TYRAMINE, 0.2 MG PER KG, IV. Data from 12 subjects.

TABLE III

*Reproducibility of mean arterial pressure response to tyramine**

Subject	Peak MAP rise			MAP curve area		
	Day 1	Day 3	Difference (day 3–day 1)	Day 1	Day 3	Difference (day 3–day 1)
	mm Hg			*mm-min*		
6†	37	34	−3	60	72	+12
	33	37	+4	59	82	+23
7	61	52	−9	177	161	−16
8†	30	27	−3	50	71	+21
	26	34	+8	72	84	+12
9	50	48	−2	153	167	+14
10	51	48	−3	198	191	− 7
		Mean	−1.1		Mean	+8.4
		SD	5.5		SD	14.5

* Abbreviations as in Table II.
† Two injections of tyramine given on each day of study.

4 minutes after injection (average, 2 minutes). The pressor effect was short-lived, and the MAP had returned to preinjection levels within 5 to 10 minutes (average 5.7 minutes). There was frequently a subsequent period when MAP was 5 to 10 mm Hg below the preinjection level. The MAP has also been graphed against time and the area included between this curve and the preinjection level measured, (Figure 2) to provide an estimate of drug effect which takes account of

TABLE IV

*Effect of reserpine on resting values**

Subject	Pulse rate Day			CO Day			MAP Day			TPR Day		
	1	3	3–1	1	3	3–1	1	3	3–1	1	3	3–1
	beats/min			*L/min*			*mm Hg*			*dyne-sec-cm⁻⁵*		
Reserpine												
1	84	54	−30	3.20	2.12	−1.08	74	58	−16	1,846	2,174	+328
2	80	64	−16	4.06	3.92	−0.14	78	68	− 9	1,526	1,398	−128
3	96	80	−16	4.74	4.74	0	83	78	− 5	1,392	1,309	− 83
4				5.14	5.38	+0.24	95	82	−13	1,482	1,212	−270
5				5.10	3.22	−1.88	100	73	−27	1,569	1,803	+234
6	84	78	− 6	5.25	4.82	−0.43	81	92	+11	1,235	1,529	+294
11	64	64	0				105	75	−30			
12							97	85	−12			
Mean	81.6	68.0	−13.6	4.58	4.03	−0.55	89.1	76.5	−12.6	1,508	1,571	+ 62.5
SE			5.111			0.34			4.5			103.1
p†			> 0.05			>0.1			< 0.05			>0.5
Control												
6	95	84	−11	4.29	5.25	+0.96	112	81	−31	2,090	1,253	−837
7	68	72	+ 4	2.92	3.45	+0.53	78	72	− 6	2,130	1,678	−452
8	64	68	+ 4	4.97	4.77	−0.20	86	104	+18	1,852		
9	75	70	− 5	4.97	4.77	−0.20	82	84	+ 2	1,323	1,406	+ 83
10	88	84	− 4	5.05	5.10	−0.05	99	103	+ 4	1,586	1,618	+ 32
Mean	78.0	75.6	− 2.4	4.31	4.64	+0.33	91.4	88.8	− 2.6	1,796.2	1,488.8	−293.5
SE			2.9			0.28			8.1			233.5
p†			> 0.4			>0.4			> 0.7			>0.2

* Abbreviations as in Table II. MAP values differ in some cases from those in Table II, since they represent values at slightly different times.
† Paired *t* test.

TABLE V

*Effects of reserpine on tyramine response**

	Change produced by tyramine Day 1					Change produced by tyramine Day 3					Difference Day 3–day 1		
	Pulse	CO	Peak rise MAP	Area	TPR	Pulse	CO	Peak rise MAP	Area	TPR	Peak rise MAP	Area	TPR
Subject	*beats/min*	*L/min*	*mm Hg*	*mm-min*	*dyne-sec-cm⁻⁵*	*beats/min*	*L/min*	*mm Hg*	*mm-min*	*dyne-sec-cm⁻⁵*	*mm Hg*	*mm-min*	*dyne-sec-cm⁻⁵*
Reserpine													
1	−20	−0.60	62	270	+1475	+ 8	+0.56	20	77	+ 70	−42	−193	−1405
2	−12	+0.10	25	80	+ 679	− 9	+0.64	15	27	+180	−10	− 53	− 499
3	+16	+0.08	67	217	+1098	+10	−0.08	50	125	+495	−17	− 92	− 603
4		−1.01	22	62	+ 652		−0.00	10	26	+ 53	−12	− 36	− 599
5		−2.19	43	224	+2426		−0.28	31	165	+862	−12	− 59	−1564
6	+15 −15	+0.23	34	72	+ 371	+12	+0.01	17	33	+133	−17	− 39	− 238
11	+26		80	254		− 4		24	53		−56	−201	
12			35	75				15	37		−20	− 38	
Mean		−0.56	46.0	156.7	+1116.8		+0.14	22.8	67.9	+298.8	−23.3	− 88.8	− 818
SE											6.76	24.43	218.4
p†											< 0.01	<0.01	<0.01
Control													
6	+25 −15	+0.31	37	60	+ 262	+15 −15	+0.23	34	72	+371	− 3	+ 12	+ 109
7	−22	−0.64	61	177	+2145	− 8	+0.43	52	161	+1003	− 9	− 16	−1142
8	+20		30	50		+20		27	71		− 3	+ 21	
9	−27	+1.56	35	153	− 37	−18	+2.33	48	167	−166	+13	+ 14	− 129
10	−25	+0.82	52	198	+ 281	−28	+0.58	48	191	+857	− 4	− 7	+ 576
Mean		+0.51	43.0	127.6	+ 662.7		+0.60	41.8	132.4	+516.5	− 1.2	+ 4.8	− 146.5
SE											3.7	6.96	362.6
p†											> 0.7	> 0.4	> 0.7

* Abbreviations as in Table II.
† Paired *t* test.

duration of response. The average area in the 12 subjects was 152 mm-minutes, SD 82.3; expressing area in this unit of mm Hg against time in minutes would permit comparison of this work by others. The reproducibility of the blood pressure response is illustrated by the data in Table III. In seven pairs of observations on the five control subjects, the mean difference in peak rise of MAP between the two studies was − 1.1 mm Hg, SD 5.5; the mean difference in area was + 8.4 mm-minutes, SD 14.5.

Cardiac output. The values for CO were generally lower than those usually quoted for dilution methods, but the subjects had been in-patients for a considerable time and were in an almost basal condition with low MAP's giving calculated preinjection TPR's in the usual normal range. With the same methods, estimates of CO as high as 15 L per minute have been made in abnormal patients not included in this study. The CO at 1½ minutes after tyramine was measured in 11 of the 12 subjects; the changes were not consistent in direction. In 5 of the 11 subjects, the change exceeded the 95% confidence limits, and of these, two were increases and three decreases.

Total peripheral resistance. At 1½ minutes after the injection, the calculated TPR was greater than the preinjection level in 9 of the 11 subjects. The remaining two were unchanged. The mean increase for the whole group was 876 dyne-sec-cm⁻⁵. Five minutes after the injection, there was no significant difference from the preinjection level.

II. Effects of reserpine on resting values.

Eight subjects received reserpine. Three of them complained of a "washed-out feeling," the other five appeared untroubled by the drug. Data used in these comparisons together with data from the five untreated controls are listed in Table IV.

Pulse rate. Resting pulse rate fell by an average of 13.6 beats per minute and was significant

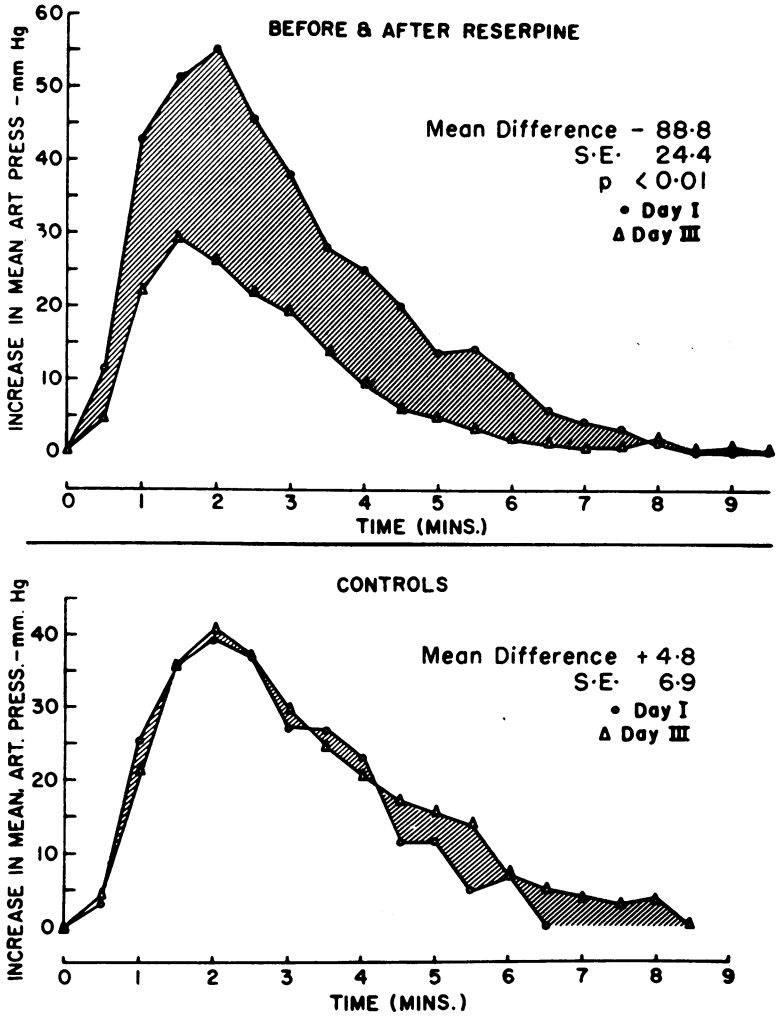

FIG. 3. AVERAGE RESPONSE TO TYRAMINE, 0.2 MG PER KG, IV. Above: before and after reserpine; data from eight subjects. Below: controls on days 1 and 3; data from five subjects. Shaded areas represent differences in response on the two days.

at the 5% level. In three out of five control subjects who received no reserpine, however, the pulse rate also fell (average, 2.4 beats per minute), but was not significantly different.

Blood pressure. In seven out of eight subjects the resting MAP was lower after reserpine. The average difference for all eight was − 12.6 mm Hg and was significant at the 5% level. In contrast, in five control subjects not receiving reserpine, the resting MAP fell in two but rose in three; the average difference of − 2.6 mm Hg was not significant.

Cardiac output. Five of the six reserpinized subjects on whom there is complete CO data had a fall in CO, but in only two of these was the change beyond the 95% confidence limits of the method. The mean difference before and after reserpine of − 0.55 L per minute was not significant.

Total peripheral resistance. The effect of reserpine on the calculated TPR was variable. TPR values after reserpine were higher in three out of six subjects and lower in the other three. Mean difference was + 62.5 dyne-sec-cm^{-5}. Two of the four control subjects showed a substantial decline on the second occasion; the other two had a slight increase. Thus no consistent change was observed in either group.

Valsalva maneuver. Seven subjects performed a Valsalva maneuver before and after reserpine. Before reserpine, the overshoot usually seen at the conclusion of apnea was observed in only two subjects; in both of these, as well as the other five, it was not seen after reserpine.

III. Effects of reserpine on the response to tyramine

A comparison was made between the tyramine responses before and after reserpine by using a paired *t* test. To exclude systematic error unrelated to reserpine administration, the result was contrasted with that of a similar comparison in the control subjects. The data are presented in Table V.

Pulse rate. No consistent modification of pulse rate response to tyramine appeared to follow reserpine, but the changes were smaller.

Blood pressure. Reserpine did not change the form of the pressor response to tyramine, but reduced its magnitude. The average peak MAP rise on day 1 was 46.0 mm Hg and on day 3, 22.8 mm Hg. The difference of − 23.2 mm Hg was significant at the 1% level. The mean area of the MAP curve before reserpine was 156.7 mm-minutes and after was 67.9 mm-minutes; the difference of − 88.8 mm-minutes was significant at the 1% level (Figure 3).

In contrast, in paired observations on the five control subjects, the average peak MAP rise on day 1 was 43.0 mm Hg and on day 3, 41.8 mm Hg. The difference of −1.2 mm Hg was not significant. The mean area on day 1 was 127.6 mm-minutes and on day 3, 132.4 mm-minutes; the difference was + 4.8 mm-minutes and was not significant.

Cardiac output. The changes in CO produced by tyramine in the reserpine-treated subjects were as variable as before reserpine.

Total peripheral resistance. After reserpine the rise in calculated TPR produced by tyramine was less than before reserpine in all six subjects. The reduction in response was significant at the 1% level.

DISCUSSION

Interest in tyramine dates from the early period of the study of sympathomimetic amines (15). Although the pharmacological action and structure of tyramine resemble that of norepinephrine, important differences in its actions can be demonstrated. Denervation of the cat nictitating membrane results in supersensitivity to injected norepinephrine but subsensitivity to injected tyramine (16). Also, animals depleted of catecholamines by reserpine pretreatment are no longer sensitive to tyramine, but remain responsive to epinephrine (13). These observations led Burn and Rand (13) to hypothesize that tyramine acted indirectly by releasing endogenous tissue catecholamine. Subsequently it has been shown (17) that the cat nictitating membrane pretreated with reserpine was subsensitive to tyramine and that this was related to depletion of norepinephrine stores. Thus, the available evidence is compatible with the suggestion that tyramine exerts its sympathomimetic effects by liberating norepinephrine from peripheral stores.

It has been further hypothesized (18–19) that catecholamine stores are contained in two compartments, a smaller store of "available" norepinephrine liberated by tyramine and a larger store of bound catecholamines which is depleted by reserpine. In guinea pig atria (19) it has been demonstrated that 50% depletion of catecholamines by reserpine produced a slightly reduced response to tyramine, but a 50% reduction of the tyramine response occurred with decrease of the normal noradrenaline content to 10%. Such observations have not been made for tissues other than cardiac tissue. Although the observations of Gaffney, Morrow, and Chidsey (20) suggest that most of the cardiac effects of tyramine result from release of myocardial catecholamines, the exact role played by release of catecholamines from different tissues in the total biological response to tyramine remains to be worked out. It is unlikely that such direct evidence will be available in man, although the work of Crout, Muskus, and Trendelenburg (19) might suggest that the doses of reserpine used in this study have resulted in depletion of more than 50% of the norepinephrine store.

Although tyramine was used for a time as a morphine antagonist in obstetric practice (21), it now finds no place in therapeutics. Apart from the studies reported by Hewlett (22) and Meyer

and Eckers (23), there appear to have been no data available on its effect in man until recently (24, 25). Tyramine is unlikely to replace presently used pressor agents in treatment, but the response to tyramine does provide a measure of the functional integrity of tissue catecholamine stores. Thus in the reserpine-treated spinal cat preparation studied by Trendelenburg (18), the responses of the nictitating membrane to sympathetic nerve stimulation and to tyramine administration showed parallel impairment over a wide range of responsiveness. It is not established that such a precise relationship holds in the intact man with the blood pressure response as the observed statistic. Nevertheless, this work has shown that the pressor response to tyramine has proved reproducible. Crandell (26) has recommended the injection of 15 mg ephedrine prior to surgery to test the availability of endogenous catecholamines and the vascular reactivity to them, but does not give details to support its validity. Furthermore, in the dog heart-lung preparation (27) and in the spinal cat preparation (28), ephedrine has been shown to have a direct action in addition to the indirect component which is abolished by reserpine. Tyramine is preferable to other indirectly acting amines such as amphetamine and metamphetamine, since its transitory action can be observed in full over the course of 5 to 10 minutes. Further study of the response to tyramine in clinical situations is necessary to establish its usefulness as such a test.

The data on the effect of reserpine on the resting state are not very striking. The cause of the fall in resting MAP is not obvious from the present studies. Reduction in the force of myocardial contraction after reserpine might be predicted from Sarnoff's (29) demonstration of the importance of catecholamines in maintaining cardiac function. However, decrease in CO in these subjects was not statistically significant, although the precision of the estimation is sufficient to detect only gross changes. Larger doses of reserpine than the moderate amounts given here, or more prolonged administration, might produce unequivocal reduction in CO. These data provide no evidence that vasodilatation and consequent lowering of TPR due to reserpine are the factors responsible for the hypotensive effect. De la Lande and associates have shown that vasodilatation (6) follows ½ to 1 hour after infusion of reserpine into the brachial artery and lasts for at least 24 hours. This vasodilatation may perhaps be responsible for the prompt hypotensive response to parenteral reserpine, which follows a similar time course, but in view of the above conclusion, it is probably not the explanation of the observations in this study.

The blood pressure response to tyramine is comparatively reproducible from day to day. In contrast, the second response to tyramine in the reserpine-treated subjects was markedly less than the first in all eight patients.

The reduction of the response to tyramine which has been demonstrated is probably due to depletion of tissue stores of norepinephrine. However, inability to release norepinephrine due to reserpine or densitization of the end organ must be considered possible. The latter is unlikely in view of the abundant animal work (30) demonstrating normal sensitivity or supersensitivity of various reserpine-treated preparations to norepinephrine as well as observations on the effectiveness of norepinephrine in reducing human forearm blood flow in reserpine-treated patients (6). The possibility that reserpine blocks the release of norepinephrine by tyramine is nowhere suggested in the work on animals and is unlikely, since at the end of 24 hours little if any reserpine would still be present in the body (31). However, it is not excluded by the present study.

SUMMARY

In eight subjects, pretreatment with reserpine, 0.06 mg per kg, produced a significant reduction in the blood pressure response to tyramine, 0.2 mg per kg, which was not observed in five control subjects. Similarly, the rise of total peripheral resistance produced by tyramine was reduced significantly by reserpine. Resting cardiac output was not altered by this dose of reserpine, but resting mean blood pressure was lowered significantly.

These observations in man are consistent with the hypothesis that tyramine acts by release of endogenous norepinephrine and that therapeutic doses of reserpine produce a reduced response to tyramine, probably by reducing endogenous catecholamine stores.

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