METABOLIC PRODUCTS OF ADRENALINE AND NORADRENALINE IN HUMAN URINE[1]

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There is little known about the metabolism of adrenaline, B.P. (epinephrine, U.S.P.) and noradrenaline, B.P. (norepinephrine, arterenol, U.S.P.) at the cellular level. However, during the past two decades much evidence has accumulated relative to the metabolic products of these two hormones.

In 1940 Richter (24) showed that by ingesting large quantities of adrenaline he could isolate from the urine a conjugate of adrenaline. He concluded that this conjugate was a sulfate. Subsequently, Beyer and Shapiro (5) performed somewhat similar experiments and concluded that the conjugate was a glucuronide. In 1947 Holtz (18) published his paper on "Urosympathin" and in 1950 (19) showed that the principal urinary catecholamine in man was noradrenaline. In 1951 von Euler (11) demonstrated hydroxytyramine, adrenaline and noradrenaline in urine.

Dodgson *et al.* (8) in 1947 showed that when *d*-adrenaline was orally administered to rabbits a conjugate of adrenaline could be isolated from the urine. Clark *et al.* (6, 7) in 1950 repeated this work and showed that rabbits metabolized *dl*- and *l*-adrenaline in a similar manner and that the conjugate formed was a glucuronide.

Then in 1952 and 1953 Schayer (25, 26, 27) published his papers on the metabolism of adrenaline. In these papers he not only showed something about the cleavage of adrenaline but pointed out that there were at least five or six urinary metabolic products of adrenaline. These papers were of particular importance in that they paved the way for future investigations in the metabolism of adrenaline and noradrenaline. In 1957, Armstrong *et al.* (1, 2) isolated 3-methoxy-4-hydroxymandelic acid from human urine and Axelrod (3, 4) isolated metadrenaline and normetadrenaline from rat urine and metadrenaline from human urine. In the same year von Euler (10) demonstrated 3,4-dihydroxymandelic acid in human urine. Subsequently, LaBrosse (21) isolated normetadrenaline from the urine of pheochromocytoma patients. Goodall *et al.* (17) and Kirshner *et al.* (20) infused human subjects with labeled adrenaline and separated and identified a number of catabolites of adrenaline. Hitherto, very little work had been done on the metabolism of noradrenaline in normal human subjects.

Metabolic products of adrenaline

Methods. Six healthy males between the ages of 20 and 35 years were infused with 5 microcuries of *dl*-adrenaline-2-C^{14} (specific activity 1.09 mc/mmol). The labeled adrenaline was mixed with 200 ml of physiological saline and infused over a period of 1 hour. The urine was collected after the infusion period, hourly for

[1] Supported by U. S. Army Contract No. DA-49-007-MD-1018.

[2] Established Investigator of the American Heart Association.

the next 5 hours, and every 6 hours for the next 18 hours, thereby affording a 24-hour collection period. The radioactivity in each sample, including a pooled 24-hour sample, was measured with a thin window Geiger tube and corrected to infinite thinness.

Separation of the urinary metabolic products was accomplished by means of a combination of ion exchange and paper chromotography. A primary column of Amberlite IRC-50 was used to absorb the basic compounds, a secondary column of Dowex-1 was used to absorb the acid catabolites and the neutral compounds passed through both columns.

In brief, an aliquot of urine containing 15,000 to 30,000 cpm was placed on the Amberlite column and then washed. This effluent was placed on the Dowex-1 column and then washed. The effluent from this latter column was collected and its radioactivity measured. The IRC-50 column was then eluted with 0.5 N acetic acid and the eluate chromatographed on Whatman #1 paper using as a solvent n-butanol saturated with N HCl. After drying, the paper was strip-cut. Each strip was eluted with water and an aliquot plated out and its radioactivity determined. Three radioactive peaks were eluted from the Amberlite IRC-50. One peak corresponds to adrenaline, another to metadrenaline and the third has not been identified.

The Dowex-1 column was attached to a fraction collector and eluted first with 0.3 M ammonium acetate buffer, pH 4.8. Three ml fractions were collected and the radioactivity in each fraction was determined. One distinct radioactive peak was observed. When the radioactivity had returned to background, the column was again eluted, but with 1.0 M ammonium acetate buffer. The radioactivity was followed as before and another distinct radioactive peak was obtained. This process was repeated for the third time but with 3.0 M ammonium acetate buffer. A third radioactive peak was observed. The three peaks corresponded respectively to a conjugate of metadrenaline, 3-methoxy-4-hydroxymandelic acid, and 3,4-dihydroxymandelic acid.

Results. Figure 1 represents the recovery of radioactivity in the urine after an infusion of *dl*-adrenaline-2-C^{14}. From this graph it is seen that 73 $\pm$ 2% of the infused radioactivity is recovered within 24 hours. These results are similar to those of Resnick and Elmadjian (23) who recovered 90% of the radioactivity within 30 hours.

Table 1 shows the distribution of radioactivity in the 24-hour urine following an infusion of *dl*-adrenaline-2-C^{14} in six human subjects. The figures represent the percentage of total radioactivity which appeared in the urine. The metabolic products eluted from the Amberlite IRC-50 are adrenaline, metadrenaline and an unknown. The amount of radioactive adrenaline, metadrenaline and the unknown is very much the same from subject to subject. However, in terms of total radioactivity the amount is quite small, *i.e.*, 4% of the radioactivity was adrenaline, 5% was metadrenaline and 1% was an unidentified compound.

The Dowex-1 fractions are metadrenaline conjugate, 3-methoxy-4-hydroxymandelic acid and 3,4-dihydroxymandelic acid. Of the Dowex-1 fractions, the largest single metabolic product is metadrenaline conjugate which represents

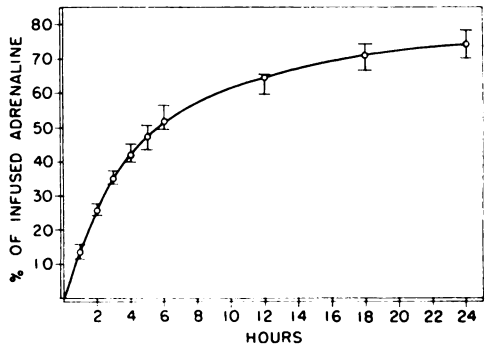

FIG. 1. Excretion of radioactivity in the urine after infusion of adrenaline-2-C^{14}. The points represent the average of 6 subjects. The vertical line represents the variation.

42 ± 3% of the total radioactivity. Kirshner *et al.* (20) showed that in man this conjugate was a sulfate rather than a glucuronide. The second largest fraction is the 3-methoxy-4-hydroxymandelic acid which represents 27 ± 2% of the total radioactivity. The 3,4-dihydroxymandelic acid represents 12 ± 2% of the total radioactivity; however, some of the radioactivity measured in this fraction represents at least one other unidentified compound. The percentages of radioactivity in the metadrenaline conjugate, 3-methoxy-4-hydroxymandelic acid, and in the 3,4-dihydroxymandelic acid fraction differ from each other but are similar from subject to subject. The Dowex effluent which represented the neutral compounds contains approximately 3% of radioactivity and this percentage is essentially the same in all six subjects.

Since completing the original adrenaline infusion experiments described in Tables 1, 2, and 3, we find that the metadrenaline conjugate fraction can be broken down into two fractions, *i.e.*, a metadrenaline conjugate and an unidentified compound. This therefore means that the 42 ± 3% (see Tables 1 and 2) of total radioactivity described under metadrenaline conjugate actually represents approximately 30% metadrenaline conjugate and 12% an unidentified compound. Similar changes hold true for the metadrenaline conjugate fraction described under Table 3.

Amine oxidase has for many years been considered an important enzyme in the inactivation of adrenaline, though by no means considered the only or the principal one. In view of the role of amine oxidase in the inactivation of adrenaline, experiments were undertaken to see if this enzyme effected any change in the excretion of the catabolites of adrenaline. Therefore iproniazid (Marsilid), an amine oxidase inhibitor, was administered to the same 6 subjects described in Table 1. Marsilid, 50 mg, was administered 4 times per day for 2, 3, 4 days, and for 2, 3, 4 weeks.

Table 2 shows the average distribution of radioactivity in the 24-hour urine following an infusion of *dl*-adrenaline-2-C^{14} in normal human subjects and the same subjects maintained on Marsilid. The control figures represent the average of the 6 subjects seen in Table 1. The second line on Table 2 represents Marsilid

TABLE 1

Distribution of radioactivity in the 24-hour urine following the infusion of dl-adrenaline-2-C^{14} in human subjects

Figures represent per cent of total radioactivity which appeared in urine.

Subject	IRC-50 Fractions				Dowex-1 Fractions			Dowex-1 Effluent	% Recovery of Radioactivity in Urine	% Recovery of Radioactivity Infused
	Total	Adr.	Metadr.	Unknown	(Metadr. conjug.) 0.3 M	(MOMA) 1.0 M	(DOMA) 3.0 M			
1. M.W.	11	4	5	2	43	27	16	2	99	70
2. E.K.	12	4	5	1	52	23	9	3	99	65
3. J.S.	14	5	6	2	39	29	8	3	93	75
4. E.M.	10	4	5	1	46	24	8	4	92	72
5. R.S.	10	3	5	1	35	31	14	3	93	78
6. J.C.	12	4	4	1	35	29	18	2	96	76
Average	12±1	4±0	5±0	1±0	42±3	27±2	12±2	3±0	95±4	73±2

TABLE 2

Distribution of radioactivity in the 24-hour urine following infusion of dl-adrenaline-2-C^{14} in normal human subjects and subjects maintained on Marsilid

Figures represent per cent of total radioactivity which appeared in the urine.

Subject	IRC-50 Fractions				Dowex-1 Fractions			Dowex-1 Effluent	% Recovery
	Total	Adr.	Metadr.	Unknown	(Metadr. conjug.) 0.3 M	(MOMA) 1.0 M	(DOMA) 3.0 M		
Controls	12±1	4±0	5±0	1±0	42±3	27±2	12±2	3±0	95±4
Marsilid 2, 3, 4 days	14±1	5±1	7±0	2±0	55±4	10±0	5±1	5±1	88±6
Marsilid 2, 3, 4 weeks	10±0	4±0	4±1	1±0	62±8	7±2	6±1	4±1	90±6

administered for 2, 3, 4 days, and the third line represents Marsilid administered for 2, 3, 4 weeks. The same metabolic products eluted from the IRC-50 column are observed: adrenaline, metadrenaline and an unknown. There was no increase or decrease in these compounds after Marsilid administration. However, the Dowex-1 fractions were greatly altered after Marsilid administration. The radioactivity in the metadrenaline conjugate fraction increased from 42 ± 3% to 62 ± 8%, whereas the radioactivity in the 3-methoxy-4-hydroxymandelic acid decreased from 27 ± 10% to 7 ± 2% and in the 3,4-dihydroxymandelic acid fraction, it decreased from 12 ± 2% to 6 ± 1%. There was no apparent change in the Dowex-1 effluent. In view of the role of amine oxidase in the oxidative deamination of adrenaline or noradrenaline and metadrenaline or normetadrenaline (see Figure 2), it would seem that with Marsilid administration there should be an increase in the metadrenaline conjugate and a decrease in the 3-methoxy-4-hydroxymandelic acid and the 3,4-dihydroxymandelic acid.

Table 3 represents the hourly distribution of radioactivity in urine samples

TABLE 3

Hourly distribution of radioactivity in urine samples following infusion of dl-adrenaline-2-C^{14} in human subject

Figures represent per cent of total radioactivity which appeared in the urine.

Hours Collected	% of Total Infused	IRC-50 Fractions				Dowex-1 Fractions			Dowex-1 Effluent	% Recovery
		Total	Adr.	Metadr.	Unknown	(Metadr. conjug.) 0.3 M	(MOMA) 1.0 M	(DOMA) 3.0 M		
1	11.3	47.5	22.0	18.0	4.0	18.9	27.6	10.1	1.8	106.0
2	15.1	5.2	0.8	3.0	0.9	38.4	46.8	22.1	1.6	114.0
3	8.9	2.7	0.4	1.2	0.8	45.6	30.9	21.2	1.9	102.0
4	8.1	3.2				55.4	23.7	15.6	2.3	100.0
5	5.4	1.9				52.4	23.2	20.2	3.8	101.5
6	4.1	2.3				50.6	19.2	12.3	3.1	87.5
6–12	10.2	1.9				43.7	12.4	14.3	5.6	77.9
12–18	4.3	1.0				49.0	2.5	3.7	20.0	77.2
18–24	5.2	2.3				39.9	7.2	7.2	20.9	77.5

following an infusion of *dl*-adrenaline-2-C^{14} in a single human subject. Though this table represents the 24-hour excretion pattern of adrenaline catabolites in a single subject, this pattern was similar to that of the other 5 subjects. Elution from the IRC-50 column yielded adrenaline, metadrenaline and an unknown. The radioactivity in the adrenaline, metadrenaline and the unknown was greatest immediately after the infusion and rapidly decreased thereafter, such that by the fourth hour after the infusion there were only trace amounts; for example, within 4 hours the radioactivity in the adrenaline decreased from 22% to trace amounts, the metadrenaline from 18% to trace amounts, and the unknown from 4% to trace amounts.

The Dowex-1 fractions presented an entirely different story. The radioactivity in the metadrenaline conjugate increased for the first 4 or 5 hours and then appeared to plateau. The radioactivity in the 3-methoxy-4-hydroxymandelic acid increased for the first 2 hours after the infusion and then gradually decreased for the next 22 hours; the 3,4-dihydroxymandelic acid excretion pattern was rather similar to that of the 3-methoxy-4-hydroxymandelic acid. As for the radioactivity in the Dowex-1 effluent, this was 2 to 5% during the first 12 hours of collection.

Metabolic products of noradrenaline

In 1946 von Euler (9) showed that sympathetic nerves contained relatively large amounts of noradrenaline and small amounts of adrenaline; this finding led him to postulate that noradrenaline was the neurotransmitter substance of the sympathetic nerves. Since then much circumstantial evidence has accumulated to support this concept (12, 13, 14, 22); and in 1958 Goodall and Kirshner (15) showed that the sympathetic nerves and ganglia could synthesize noradrenaline but were incapable of synthesizing any significant amounts of adrenaline. In view of this, the metabolic products of noradrenaline then take on a particular

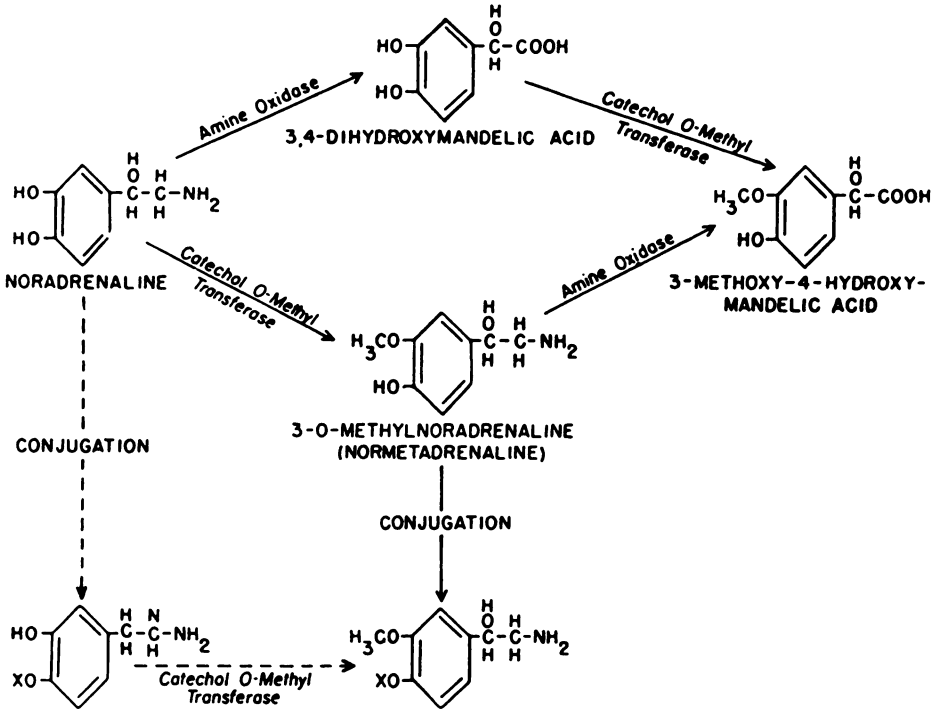

FIG. 2. Schematic presentation of the possible pathways through which noradrenaline may be metabolized.

importance since these products could represent a means by which the normal physiological functioning of the sympathetic nervous system could be measured; and, too, a means by which those clinical conditions which represent an aberration in the physiology of the sympathetic nervous system could be more critically studied, *i.e.*, chronic postural hypotension, sympathetic nerve tumors, diabetic neuropathy, anorexia nervosa, certain types of hypertension, etc.

Method. The method used has been described in detail by Goodall *et al.* (16) and therefore will be only summarized in this paper. Six males between 20 and 35 years of age were infused with 9.5 microcuries of *dl*-noradrenaline-2-C^{14} (specific activity 20 mc/mmol). The labeled noradrenaline was mixed with 250 ml of physiological saline and infused over a period of 1 hour. The urine was collected at the end of the infusion period and hourly thereafter for the next 5 hours, and then every 6 hours for the next 18 hours, thereby affording a 24-hour sample.

The catabolites of noradrenaline were separated by means of a combination of ion exchange and paper chromatography. In brief, a primary column of Amberlite IRC-50 was used in conjunction with a secondary column of Dowex-1. An aliquot of urine containing 15,000 to 30,000 cpm was placed on the Amberlite

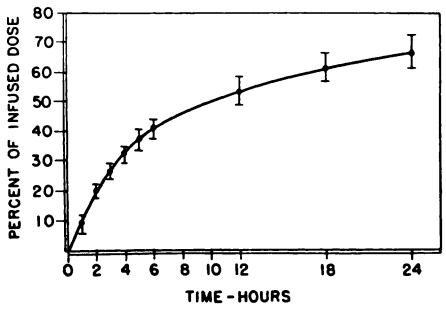

FIG. 3. Excretion of radioactivity in the urine after infusion of noradrenaline-2-C^{14}. The points represent the average of 6 subjects. The vertical lines represent the variation.

and then washed. The effluent from the Amberlite was then placed on the Dowex-1 column and washed. The basic compounds which were absorbed on the Amberlite IRC-50 were eluted with 0.5 N acetic acid. These were separated by paper chromotography, identified and their radioactivity measured. The acid compounds absorbed on the Dowex-1 column were eluted with ammonium acetate buffer pH 4.8 of varying molarity. The various Dowex-1 fractions were collected and identified by comparing with known compounds. All radioactivity was measured with a thin window Geiger tube and corrected to infinite thinness.

Results. Figure 2 is a schematic presentation of the possible pathways through which noradrenaline may be metabolized. Obviously, similar pathways could hold for the metabolism of adrenaline. Evidence for the pathway is largely predicated upon the work of Axelrod *et al.* (3, 4), Armstrong *et al.* (2), von Euler (10), Goodall *et al.* (16, 17), and Kirshner *et al.* (20).

Figure 3 is a graph illustrating the excretion rate of radioactivity in urine after an infusion of *dl*-noradrenaline-2-C^{14}. The points represent the average of 6 subjects and the vertical lines represent the variations. In 24 hours, 67 ± 4% of the radioactivity was recovered.

Table 4 shows the distribution of radioactivity in the 24-hour urine following the infusion of *dl*-noradrenaline-2-C^{14} in 6 subjects. The figures represent the percentage of total radioactivity which appeared in the urine. The IRC-50 elution yielded three compounds: noradrenaline, normetadrenaline and an unidentified compound. These represented only a small amount of the total radioactivity, *i.e.*, 4 ± 1% of noradrenaline, 3 ± 1% of normetadrenaline and 2 ± 1% of the unknown. The Dowex-1 elutions yielded a total of 6 catabolites; 3 identified and 3 unidentified. The 0.05 M eluate yielded a conjugate of normetadrenaline which appears to be a sulfate. The catabolite resulting from the 0.3 M elution has not been identified. The 1.0 M eluate produced the 3-methoxy-4-hydroxymandelic acid. The 3.0 M elutions (A and B) yielded 2 radioactive compounds with each elution, *i.e.*, 3,4-dihydroxymandelic acid and an unidentified compound. From the Dowex-1 fraction it is apparent that the biggest single metabolic product of noradrenaline is the 3-methoxy-4-hydroxymandelic acid and that this represents 32 ± 3% of the total radioactivity. The conjugate of normetadrenaline was the

TABLE 4

Distribution of radioactivity in the 24-hour urine following the infusion of dl-noradrenaline-2-C^{14} in human subjects

Figures represent per cent of total radioactivity which appeared in urine.

Subjects	IRC-50 Fractions				Dowex-1 Fractions					Dowex Effluent	% Recovery Urinary-C^{14}	% of Infused Dose Recovered
	Total	Nor.	NMA	Unknown	0.05 M Eluate NMAX	0.30 M Eluate Unk.	1.0 M Eluate MOMA	3.0 M(A) Eluate DOMA + Unk.	3.0 M(B) Eluate DOMA + Unk.			
MA	10	4	3	2	17	9	30	8	16	3	93	62
SN	8	2	2	3	20	10	33	12	12	4	99	69
LO	12	4	3	3	21	7	38	11	9	5	103	64
BO	9	4	3	2	22	13	30	10	11	4	99	72
WE	11	3	4	2	20	10	30	12	14	5	102	65
MR	9	4	2	2	16	8	29	12	13	3	90	67
Average	10±2	4±1	3±1	2±1	19±2	10±2	32±3	11±2	13±2	4±1	98±5	67±4

TABLE 5

Excretion of noradrenaline and its metabolic products during the 24-hour period following an infusion of dl-noradrenaline-2-C^{14} in human subject

Figures represent per cent of total radioactivity which appeared in the urine.

Time in Hours	IRC-50 Fractions				Dowex-1 Fractions					Dowex Effluent	% Recovery Urinary-C^{14}	% of Infused Dose Recovered
	Total	Nor.	NMA	Unknown	0.05 M Eluate NMAX	0.30 M Eluate Unk.	1.0 M Eluate MOMA	3.0 M(A) Eluate DOMA + Unk.	3.0 M(B) Eluate DOMA + Unk.			
1	38	16	12	8	10	2	33	4	8	4	86	11
2	9	3	4	1	15	7	41	11	9	5	98	10
3	3	1	1	0.4	24	12	37	8	19	3	107	7
4	3	1	1	0.4	26	11	30	8	21	4	102	6
5	2	0.7	0.7	0.5	21	8	29	12	22	4	97	5
6	2	0.9	0.7	0	26	7	22	19	17	4	98	4
6–12	2	Trace	0	0	33	15	16	12	17	3	98	10
12–18	1	0	0	0	33	11	18	13	20	3	99	7
18–24	2	0	0	0	19	8	16	12	15	11	83	5

second largest fraction and represented 19 ± 2%. The 1.0 M eluate and the 3.0 M eluates (A and B) showed respectively 10 ± 2%, 11 ± 2% and 13 ± 2% of radioactivity. The Dowex effluent showed only 4 ± 1% of the total radioactivity. The excretion pattern of the various catabolites of noradrenaline was similar in all 6 subjects.

Table 5 represents the excretion of noradrenaline and its metabolic products in the 24-hour period following an infusion of *dl*-noradrenaline-2-C^{14} in a single human subject. The figures represent the percentage of total radioactivity which appeared in the urine. Though this table demonstrates the 24-hour pattern of noradrenaline catabolite excretion of a single individual, it is similar to that of

the other 5 individuals. As before, the IRC-50 fractions were noradrenaline, normetadrenaline and an unknown. The amount of radioactive noradrenaline, normetadrenaline and the unknown was highest immediately after the infusion but rapidly decreased thereafter such that by the 6- to 12-hour period there were only trace amounts of each of these compounds. Immediately after the infusion, the radioactivity of the noradrenaline was 16%, the normetadrenaline was 12% and the unknown 8%.

As for the Dowex-1 fraction, the radioactivity of the normetadrenaline conjugate gradually increased from 10% following the infusion to 33% during the 6- to 18-hour period. The radioactivity in the unidentified catabolite (0.3 M eluate) increased from 2% after the infusion to approximately 12% by the end of the third hour, and thereafter remained between 7% and 15%. The radioactivity in the 3-methoxy-4-hydroxymandelic acid fraction increased from 33% to 41% in the first 2 hours after the infusion and then gradually decreased over the next 22 hours. As for the 3.0 M eluates (A and B) which include the 3,4-dihydroxymandelic acid, the radioactivity apparently increased for the first 4 or 5 hours and then gradually decreased. The radioactivity of the Dowex effluent varied between 3% and 5% during the first 18 hours of collection.

Summary

1. *dl*-Adrenaline-2-C^{14} and *dl*-noradrenaline-2-C^{14} were infused in 12 healthy males and the urine collected hourly thereafter for 24 hours.

2. The urinary catabolites of adrenaline and of noradrenaline were separated by means of a combination of ion exchange and paper chromatography. Radioactivity of each catabolite was measured with a thin window Geiger tube and corrected to infinite thinness.

3. After an infusion of labeled adrenaline, 73 ± 2% of the radioactivity was recovered in 24 hours, and after an infusion of labeled noradrenaline, 67 ± 4% of the radioactivity was recovered in 24 hours.

4. Distribution of radioactivity in the 24-hour urine following an infusion of labeled adrenaline was: adrenaline, 4 ± 0%; metadrenaline, 5 ± 0%; unidentified compound, 1 ± 0%; metadrenaline conjugate fraction, 42 ± 3%; 3-methoxy-4-hydroxymandelic acid, 27 ± 2%; 3,4-dihydroxymandelic acid plus unidentified compound, 12 ± 2%.

5. Distribution of radioactivity in the 24-hour urine following an infusion of labeled noradrenaline was: noradrenaline, 4 ± 1%; normetadrenaline, 3 ± 1%; unidentified compound, 2 ± 1%; normetadrenaline conjugate, 19 ± 2%; unidentified compound, 10 ± 2%; 3-methoxy-4-hydroxymandelic acid, 32 ± 2%; 3,4-dihydroxymandelic acid plus two unidentified compounds, 11 ± 2% and 13 ± 2%.

6. The role of the metabolic products of noradrenaline as a possible barometer of the physiological functioning of the sympathetic nervous system is discussed.

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