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*NOR*ADRENALINE OUTPUT IN URINE AFTER INFUSION IN MAN

BY

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*Nor*adrenaline is normally excreted in human urine in amounts of some 20–40 μg. per day (Kroneberg and Schümann, 1950 ; Euler and Hellner, 1951a). Under certain conditions the output is increased, e.g., during heavy muscular work (Euler and Hellner, 1951b) and in phaeochromocytoma (Engel and Euler, 1950), where it may attain values of more than 2,000 μg. per day.

In order to study the excretion in relation to administered *nor*adrenaline in man we have infused the hormone at a fixed rate intravenously and analysed the urine for *nor*adrenaline and adrenaline.

Six experiments were carried out on four subjects. Cases 1 and 2 were patients with morbus Addison and subjects 3 and 4 were healthy medical students, whose co-operation is gratefully acknowledged. *dl-Nor*adrenaline hydrochloride, dissolved in normal saline, was infused intravenously at a rate of 16.4–28 μg. per min. Urine was collected for a period immediately before infusion, during infusion, and, in two experiments, immediately after infusion.

The catechol amines from the urine were prepared and analysed according to the method of Euler and Hellner (1951a). The recovery of *nor*adrenaline and adrenaline can be estimated at about 70 per cent.

In order to split conjugated *nor*adrenaline and adrenaline the urine was hydrolysed at *p*H 2 for 20 min. at 100° before the absorption of the catechol amines. 1 ml. 20 per cent aluminium sulphate was added per 100 ml. urine ; 0.5 N-NaOH was then added dropwise under continuous stirring until *p*H 7.6 was reached and the aluminium hydroxide formation was complete. The precipitate was allowed to settle and then filtered off, washed twice with distilled water, and dissolved in 2 N-H_2SO_4. The solution containing the dissolved precipitate was then adjusted to *p*H 3.5 with 0.5 N-NaOH. Four volumes of equal parts of ethanol and acetone were then added in order to precipitate the salts. The solution was left in the refrigerator for some hours, filtered, and the filtrate evaporated *in vacuo* to a small volume. The final extract was made up to correspond to 5–25 ml. original urine per ml. and *p*H adjusted to 4. This extract could be tested directly biologically and showed no actions other than those of the catechols present.

The biological estimation was made on the cat's blood pressure and on the fowl's rectal caecum, according to the method described by Euler (1949).

The assay of the urinary extract was made in terms of *l-nor*adrenaline and *l*-adrenaline hydrochloride. Since the activity of the *dl-nor*adrenaline is approxi-

TABLE I

Subject	Infused *dl-nor*adr. μg./min.	Time min.	Vol. ml.	Excreted		% adr.	Extra output of *l-nor*adr. μg./min.	% output of infused *nor*adr.
				l-adr. μg./min.	*l-nor*adr. μg./min.			
1*a*. (D.):								
Before infusion		115	102	0.0077	0.0178	30		
During infusion	16.4	35	74	0.019	0.138	12	0.120	1.5
1*b*. (D.):								
Before infusion		50	134	0.012	0.0094	57		
During infusion	16.7	50	205	0.0115	0.201	5.5	0.192	2.3
2*a*. (S.):								
Before infusion		33	80	0.011	0.0213	33		
During infusion	17.7	65	345	0.0125	0.314	3.8	0.293	3.3
2*b*. (S.):								
Before infusion		90	590	0.0086	0.015	36		
During infusion	16.4	60	265	0.009	0.217	4	0.202	2.5
3. (K.L.):								
Before infusion		78	56	0.0079	0.0255	24		
During infusion	24.6	65	360	0.0266	0.266	9	0.240	2.0
After infusion		45	116	0.016	0.071	18		
4. (A.K.):								
Before infusion		79	380	0.0212	0.060	26		
During infusion	28.0	61	600	0.053	0.413	11	0.353	2.5
After infusion		59	140	0.027	0.056	33		

Figures are given in terms of *l-nor*adrenaline hydrochloride.

mately one half of that of *l-nor*adrenaline the former figures have been halved for the computation of the output percentage. The error introduced by this approximation is small. The results are given in Table I.

In all experiments there was about a tenfold increase in the amount of *nor*adrenaline excreted per minute during the infusion. From the increased output of *nor*adrenaline compared with that normally found it appears that 1.5–3.3 per cent of the amount administered per minute was recovered from the urine. The recovery percentage indicates that the inactivation was rather effective. In the period after termination of the infusion the *nor*adrenaline figure was still distinctly increased, although considerably less than during infusion.

Discussion

*Nor*adrenaline infusion of the same order of magnitude as in the present experiments, viz., some 0.1–0.2 μg. *l-nor*adrenaline per kg. per min., generally causes a rise of blood pressure (Goldenberg, Pines, Baldwin, Greene, and Roh, 1948, and others). Such an effect was also noted in the present experiments. The relatively large increase in *nor*adrenaline excretion indicates that the normal inflow of *nor*adrenaline into the circulation is much lower than that administered. Unfortunately it has not been possible to obtain reliable figures for the blood or plasma

concentration of *nor*adrenaline during the infusion. Such a figure would have permitted determination of the inactivation rate and perhaps also have given some idea of the normal *nor*adrenaline concentration in plasma. In human whole blood a figure of 1–2 μg. *l-nor*adrenaline per 100 ml. has been observed (Euler and Schmiterlöw, 1947), but this may be too high owing to the fact that *nor*adrenaline is taken up by the blood corpuscles (Bain, Gaunt, and Suffolk, 1937).

It is of interest to compare the excretion of *nor*adrenaline during infusion at a known rate with the excretion determined in cases of phaeochromocytomas, in which condition the excretion has amounted to 0.3–1 μg. per min. (Engel and Euler, 1950). The figure 0.3 μg. is about equal to the highest obtained during infusion in the present experiments and corresponds to an inflow of some 9 μg. *l-nor*adrenaline per min. or about 0.15 μg. per kg. per min. This amount generally raises the systolic blood pressure some 30–40 mm. in normal subjects, but may have a much stronger action in hypertensives (Goldenberg *et al.*, 1948).

If the relation between input and output is similar during normal conditions, without extra administration of *nor*adrenaline, as in the case outlined above, the normal output in the urine of some 0.02 μg. *l-nor*adrenaline per min. during rest would mean that about 0.6 μg. *l-nor*adrenaline per min. was entering the general circulation. Such a figure is not incompatible with the experimental results of Goldenberg and associates, who found 0.05 μg. per kg. per min.—i.e., 3 μg. per min. in a 60-kg. person—causing a slight increase in blood pressure.

The figures for adrenaline do not show any consistent changes during the infusion of *l-nor*adrenaline, which suggests that infused *nor*adrenaline is not converted into adrenaline to any appreciable extent in the body.

In the period immediately following the infusion there was still an increased output of *nor*adrenaline, although to a much smaller extent than during the infusion. This excretion may be explained either on the assumption that the bladder was not completely emptied at the end of the infusion or that some *nor*adrenaline had been taken up by the blood or by some other tissues and was being gradually liberated.

Summary

Infusion of 16.4–28 μg. *dl-nor*adrenaline per min. in two patients and two healthy subjects increased the *nor*adrenaline excretion about tenfold, without producing marked changes in adrenaline excretion.

1.5–3.3 per cent of the infused amount was found in the urine per unit of time.

From the relation of administered and excreted *nor*adrenaline it is inferred that normally some 0.5–1 μg. *l-nor*adrenaline per min. reaches the general circulation.

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