calcium carbonate or aluminium hydroxide gel by mouth (Matsumoto & Grossman, 1960) reduces the gastrointestinal blood loss caused by oral aspirin in man.

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Distribution and metabolism of dopamine in guinea-pigs

SIR,—While the tissue distribution and metabolism of noradrenaline after intravenous injection has been extensively investigated, relatively little information is available concerning the fate of its precursor dopamine shortly after injection. While investigating the possible formation of vasoactive metabolites from [2-^{14}C]dopamine in guinea-pigs, we observed that the kidneys contained a proportionately larger amount of dopamine (μg/g) than all other tissues investigated in the 5 min after its intravenous administration. In those tissues examined, more than 50% of all the dopamine was metabolized to acidic metabolites within 1·5–2 min after its injection.

Guinea-pigs anaesthetized with urethane were killed either 1·5–2 min (maximum depressor effect) or 5 min (response completed) after the intravenous injection of 250 μg/kg (5 or 10 μc) of [2-^{14}C]dopamine (Halushka & Hoffmann, 1968). Tissue extracts of samples of the heart, liver, lungs, kidneys, spleen and plasma were chromatographed on thin-layer plates for separation of the radioactive components. The procedure involved an acidified acetone precipitation followed by a butanol–heptane extraction, drying of the final acid extract and the reconstitution in 250 μl of 0·01 N HCl–acetone (1 : 5). Fifty μl of the reconstituted solution was spotted onto either phosphate buffered silica gel or cellulose plates and developed with either water-saturated n-butanol–glacial acetic acid (6 : 1) or butanol–formic acid–water (15 : 3 : 2) (Holtz, Stock & Westerman, 1963).

At death the kidneys contained the highest concentration (μg/g wet weight) of radioactivity without regard to chemical species (dopamine equivalents) (Table 1). At the 1·5–2 min time interval this value was about three times greater than that in the tissue exhibiting the next highest concentration (lungs). The third highest concentration was in the liver, followed by the heart and then the plasma. In the animals killed at 5 min, the kidneys contained 6 times as much radioactivity as the lungs and the total radioactivity in the lungs and liver

TABLE 1. THE DISTRIBUTION AND METABOLISM OF [2-^{14}C]DOPAMINE INJECTED INTRAVENOUSLY IN GUINEA-PIGS

Tissue	Dopamine* equivalents	Dopamine	HVA + DPA	HVA
	1·5–2 min post injection			
Kidneys	6·21 ± 0·44	†1·50 ± 0·30 (25%)	†3·53 ± 0·69 (69%)	‡0·25 ± 0·05 (4%)
Lungs	2·12 ± 0·45	0·31 ± 0·07 (15%)	1·48 ± 0·33 (78%)	0·18 ± 0·10 (10%)
Liver	1·30 ± 0·34	0·09 ± 0·01 (9%)	0·71 ± 0·22 (76%)	0·06 ± 0·01 (7%)
Spleen¶	1·25¶	0·30 (24%)¶	0·48 (71%)¶	0·15 (13%)¶
Heart	1·19 ± 0·14	0·51 ± 0·06 (44%)	0·54 ± 0·09 (50%)	0·05 ± 0·03 (5%)
Plasma	0·27 ± 0·04	0·06 ± 0·01 (19%)	0·21 ± 0·03 (55%)	0·08 ± 0·08 (5%)
	5 min post injection			
Kidneys	6·88 ± 1·50	‡0·78 ± 0·49 (10%)	‡5·2 ± 1·0 (87%)	*f* 0·37 (6%)
Lungs	1·16 ± 0·19	0·05 ± 0·01 (5%)	0·89 ± 0·19 (89%)	0·13 (17%)
Liver	0·68 ± 0·09	0·11 ± 0·02 (18%)	0·44 ± 0·09 (72%)	0·08 (11%)
Spleen	0·54*f*	0·14 (26%)*f*	0·33 (69%)*f*	0·08 (16%)
Heart	1·18 ± 0·17	0·32 ± 0·09 (27%)	0·67 ± 0·1 (64%)	0·10 (10%)
Plasma	0·34 ± 0·07	0·03 ± 0·01 (14%)	0·24 ± 0·06 (79%)	<0·002 0%

The results are expressed in μg/g ± s.e. The numbers in ( ) represent the % of the total radioactivity (d/min) in that tissue.

* Represents the total amount of radioactivity found in the tissue at the time of death, expressed as μg/g dopamine.

† Determined in 4 guinea-pigs. ‡ Determined in 3 guinea-pigs. *f* Determined in 2 guinea-pigs.

¶ Determined in 1 guinea-pig.

HVA = homovanillic acid.

DPA = dihydroxyphenylacetic acid.

had decreased to approximately one-half that at the 1·5–2 min interval, while that in the heart and plasma remained the same. The total amount of radioactivity in the kidney increased during the interval. Despite the rapid degradation of dopamine to acidic metabolites during the first 2 min, the kidney showed the highest concentration of unchanged dopamine (1·50 μg/g) which was 3 times greater than that of the heart (0·51 μg/g). At the 5 min interval the amount of unchanged dopamine (0·78 μg/g) in the kidney was 2½ times greater than that remaining in the heart (0·32 μg/g).

Dopamine (250 μg/kg) regularly elicited a vasodepressor response of approximately 10 mm Hg in the guinea-pig. Eble (1964) has shown in dogs that the vasodepressor response to dopamine is accompanied by dilatation of the renal vascular bed with increased renal blood flow. This increased flow could explain the higher concentrations of dopamine found in the kidneys. However, its preferential uptake by the kidneys was also seen in two experiments in which 25 mg/kg, given intravenously, produced only a pressor response. At the 1·5 to 2 min time interval, after this dose, the kidneys contained at least twice as much radioactivity as any other tissue and three times as much at the 5 min interval. Again, in dogs, McNay, McDonald & Goldberg (1965), have shown that such pressor responses to high doses of dopamine were accompanied by decreased renal blood flow. Thus, the higher concentrations of dopamine in the kidneys after a vasodepressor dose (250 μg/kg) do not seem to be solely the result of an increase in the proportion of the cardiac output delivered to the kidneys as a result of the pharmacological response, since this preferential distribution was also seen with doses producing renal vasoconstriction. As a consequence of these findings, the possibility of some type of enhanced uptake of dopamine by the kidney, not dependent solely on dose or vascular response, must be considered.

It is of interest to compare the distribution of dopamine with that of noradrenaline, administered intravenously. No comparable study of noradrenaline distribution is available in guinea-pigs, however, Whitby, Axelrod & Weil-Malherbe (1961) injected [^{3}H]noradrenaline intravenously into cats and killed them 2 min later. They found the greatest amount of radioactivity regardless of the chemical nature (noradrenaline equivalents), to be in the spleen followed by the lungs, heart, adrenal glands, kidneys, liver, small intestines and plasma.

To make a comparison with their figures, the uptake of dopamine by the tissues has been ranked in the order of total radioactivity/g (dopamine equivalents) at 2 min. We found the total radioactivity to be highest in the kidney followed by the lungs, the liver, heart and spleen (1 value) and the plasma. Thus, the tissue distribution of intravenously administered dopamine differs from that of noradrenaline. The spleen, an organ of high adrenergic activity, exhibited the largest uptake of noradrenaline, while our results show that the kidney contained the highest amount of dopamine (μg/g wet weight). The lungs, heart and plasma occupied the same rank order in the distribution of both dopamine and noradrenaline. If the uptake of dopamine into various tissues was related solely to the biosynthesis of noradrenaline, then a similar rank ordering of tissue uptake should have been observed for both amines. However, the kidney accumulated more dopamine than the heart or spleen, despite its failure to take up comparable amounts of noradrenaline. This indicates that the high renal uptake of dopamine is not explicable just on the basis that it serves as a precursor of noradrenaline in this organ.

The predominant metabolite of dopamine injected intravenously was dihydroxyphenylacetic acid (DPA) with small amounts of homovanillic acid (HVA) also being found. The deaminated products at the 1·5–2 min time period represented at least 50% of the total radioactivity in the heart and reached a maximum of 78% in the lungs. At 5 min, the deaminated products represented 64% of the total radioactivity in the heart, 89% in the lungs and 87% in the kidneys, the total amount (μg/g) increasing 1·5 times in the kidneys, only slightly in the heart, and decreasing in the lungs and liver while remaining the same in the plasma. This increase in the renal content of deaminated metabolites most likely represents uptake of DPA from the blood by the kidneys reflecting in part an excretory function (Werdinus, 1967).

Only 1 to 5% of the total radioactivity in all the tissues was found to be 3-methoxydopamine. Crout (1964) determined that [^{3}H]normetanephrine represented but 1 to 3% of the total radioactivity in the heart and plasma 1 min to 4 hr after intravenous injection of [^{3}H]noradrenaline in guinea-pigs. Together with our results, it is apparent that direct *O*-methylation of catecholamines does not play a significant role in their early metabolism in this species, compared to cats and mice in which the predominant metabolite of noradrenaline is normetanephrine (Whitby & others, 1961). In addition, dopamine is much more rapidly metabolized by monoamine oxidase than is noradrenaline in guinea-pigs. One min after completion of the injection of [^{3}H]noradrenaline, depending on the dose, Crout (1964) found that from 69–93% of the radioactivity in the plasma represented the parent amine. On the contrary, we found that at the same time only 19% of the plasma radioactivity was unchanged dopamine.

Only in the heart was the formation of noradrenaline from dopamine consistently noted, being approximately 5% of the total tissue radioactivity at 5 min.

The metabolism of dopamine has also been studied in rats and mice. Twenty-four hr after the intraperitoneal administration of 300 μg of [^{14}C]dopamine to rats, 39% of the dose appeared in the urine as homovanillic acid 3·4% as dihydroxyphenylacetic acid 6·5% as 3-methoxydopamine and 6·1% was unchanged dopamine (Williams, Babuscio & Watson, 1960). Symchowicz & Korduba (1967) found that the metabolism of dopamine administered intraperitoneally was much slower in the spleen than in the heart of the mouse. It is difficult to compare the distribution and metabolism of dopamine in these investigations with the present results because the time intervals, the organs studied, the doses of dopamine and routes of administration were all different. However, it is apparent that there is a species difference in the metabolism of dopamine as well as differences in the rate of metabolism of dopamine by different organs in the same species.

It has been suggested that dopamine may have a physiological function in addition to being a precursor of noradrenaline (Wurtman, 1965; Hornykiewicz, 1966). It is the only endogenous catecholamine known to dilate the renal vasculature and occurs in concentrations of 0·02–0·04 μg/g in the kidneys of rats, guinea-pigs, rabbits, dogs and cats (Anton & Sayre, 1964) and 0·1 μg/g in dogs (Wegman, 1963). No function has been ascribed to the endogenous dopamine in the kidney. However, consideration of the fact that exogenous dopamine causes an increase in renal blood flow and glomerular filtration rate (McDonald, Goldberg & others, 1964), a sodium diuresis (Goldberg, McDonald & Zimmerman, 1963), as well as the uptake of large amounts of dopamine into the kidney with rapid metabolic degradation, is consistent with the idea that dopamine could mediate some physiological function in the kidney.

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