Preliminary observations on the metabolism of [1-^{14}C]tyramine in man

Tyramine (*p*-hydroxyphenethylamine) is a constituent of normal human urine (Perry, 1962; DeQuattro & Sjoerdsma, 1967). Alterations in its excretion occur in some pathological conditions (Levine, Oates & others, 1962; Studnitz, Käser & Sjoerdsma, 1963; Boulton, Pollit, & Majer, 1967), but the significance of the changes is unknown. Tyramine is thought to be responsible for the severe hypertensive reactions sometimes seen in patients taking monoamine oxidase inhibitors who also ingest tyramine-containing foods such as cheese, yeast extracts, and red wine (Blackwell, Marley & others, 1967). The intravenous administration of this amine is used as a diagnostic test for pheochromocytoma (Engelman & Sjoerdsma, 1964). Although the normal concentrations of urinary tyramine excreted by man and the influence of drugs on these have been examined (Perry, 1962; DeQuattro & Sjoerdsma, 1967), little is known about the metabolism of tyramine in man. Horowitz, Lovenberg & others (1964) reported that 1 to 3% of an intravenous dose of tyramine was excreted in the urine unchanged by human subjects and suggested that the rest was metabolized to *p*-hydroxyphenylacetic acid. We report here the results of a preliminary quantitative study of the metabolism of [1-^{14}C]tyramine in man.

Four healthy adult male volunteers who had received no drugs in the two months preceding the experiment received [1-^{14}C]tyramine HBr (New England Nuclear, 5·3 mCi/mmol, 50 μCi total dose) through an intravenous catheter kept open by 5% dextrose in saline according to the procedure of Engelman & Sjoerdsma (1964). Water intake was voluntarily restricted during the first 6 h after dosage; the diet was not limited in quantity but beans, bananas, and cheese were prohibited for 24 h after administration of the radioactive compound.

Amounts of radioactivity were determined by liquid scintillation counting in samples of urine, faeces, plasma, formed blood fractions and expired carbon dioxide. Radioactive metabolites in the urine were separated and measured (Tacker, McIsaac & Creaven, 1970). The amounts of *p*-hydroxyphenylacetic acid and tyramine were confirmed by isotope dilution and recrystallization to constant specific activity. [1-^{14}C]Tyramine added to urine and stored at pH less than 4 at $-10°$ showed no degradation.

Following administration of [1-^{14}C]tyramine the radioactivity was rapidly excreted, 70–90% of the total urinary radioactivity appearing in the first 6 h collection period (Table 1). The reason for the large range of urinary recovery of radioactivity is at present unknown though incomplete collection of the early samples in two subjects seems the most likely explanation. Plasma concentrations of radioactivity were 1000 $\pm$ 140, 700 $\pm$ 120, 40 $\pm$ 20, and 20 $\pm$ 0 pCi/ml at 0·5, 1, 2, and 4 h, respectively.

Table 1. *Urinary excretion of radioactivity in man after administration of* [*1-*^{14}*C*]-*tyramine.*

	Subjects				
Time (h)	1	2	3	4	Mean $\pm$ s.d.*
6	69·7†	75·3	90·0	85·5	80·1 $\pm$ 9·3
12	24·0	21·6	7·9	11·3	61·2 $\pm$ 7·9
24	4·9	1·9	1·5	2·4	2·7 $\pm$ 1·5
48	1·3	1·2	0·6	0·8	1·0 $\pm$ 0·4
72	0	0	0	0	0
96	0	0	0	0	0
% of dose	43·5	51·2	63·1	81·1	58·1 + 21·7

* Mean $\pm$ s.d. based on a group of four subjects.
† Percentage of total urinary excretion of radioactivity.

Concentrations of radioactivity in the erythrocytes were 600 ± 50 and 200 ± 0 pCi/ml at 0·5 and 1 h. The disappearance of radioactivity is thus rapid, for zero time plasma radioactivity should be in the range 14 000–20 000 pCi/ml at the dose given. Unlike 5-hydroxytryptamine (Tyce, Flock & Owen, 1968) tyramine was not concentrated by the formed elements of the blood. No significant radioactivity was found in the faeces or expired air.

Eleven radioactive compounds were found in the urine; two of these were definitely and two others tentatively identified. *p*-Hydroxyphenylacetic acid accounted for 83·8 ± 3·6% of the urinary radioactivity. Free tyramine was the next most abundant metabolite and accounted for 6·1 ± 2·6% of the urinary radioactivity. *N*-Acetyltyramine and *p*-hydroxyphenylacetaldehyde were tentatively identified, but each constituted less than 0·5% of the urinary radioactivity. The remaining seven metabolites were not identified, but the R_F values did not correspond to any of the following metabolites of tyramine identified in the urine from rats given [1-^{14}C]tyramine (Tacker & others, 1970): tyramine-*O*-glucuronide, *p*-hydroxyphenylacetyl glycine, *N*-acetyltyramine-*O*-glucuronide, *N*-acetyltyramine sulphate, tyrosol (*p*-hydroxyphenylethanol), tyrosol glucuronide and tyrosol sulphate. No correspondence was shown with 3-methoxy-4-hydroxyphenethylamine, octopamine, dopamine, noradrenaline or their acidic metabolites, homovanillic acid, *p*-hydroxymandelic acid, 3,4-dihydroxyphenylacetic acid and vanilmandelic acid which are not metabolites of tyramine in the rat.

The amount of unchanged tyramine excreted by man (6·1%) is three times that excreted by the rat (1·4%) (Tacker & others, 1970). This greater amount of unchanged amine and the absence of tyramine-*O*-glucuronide in the human urine may be attributed to species difference in the metabolism of tyramine or may reflect the different modes of administration of the amine in the two experiments. Hertting & LaBrosse (1962) found that 2% of a dose of adrenaline given to rats via the portal vein was excreted in the urine unchanged, whereas after administration into the peripheral venous circulation, 13% was excreted unchanged.

The second most abundant urinary metabolite of tyramine excreted by the rat is the glycine conjugate of *p*-hydroxyphenylacetic acid (Tacker & others, 1970). Man and certain other primates conjugate phenylacetic acid with glutamine rather than glycine (Williams, 1958), but the results of the present study support the earlier observation (Theirfelder & Sherwin, 1914) that substituted phenylacetic acids are excreted unchanged by man and demonstrate that if any glutamine conjugate is formed from the *p*-hydroxyphenylacetic acid formed from tyramine, it must constitute less than 3% of the urinary radioactivity.

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Sensitization procedures and the blood sugar concentration

It is relatively easy to induce anaphylactic shock in guinea-pigs but rats and mice are generally resistant to its development. The injection of *Bordetella pertussis* vaccine at the time of sensitization however increases the susceptibility of rats and mice (Dhar & Sanyal, 1963). Hypoglycaemia results when rats and mice are injected with *B. pertussis* vaccine (Dhar, Sanyal & West, 1967a) but it is not known whether such treatment alters the blood sugar concentration in guinea-pig, rabbits and dogs. Experiments have therefore been made to investigate the effects of *B. pertussis* vaccine, or antigen, or of both adjuvant and antigen, on the blood sugar concentrations of these animal species, and so to determine whether hypoglycaemia aggravates the symptoms of anaphylactic shock.

Groups of 8 adult animals were sensitized by an intraperitoneal injection of horse serum (1 ml in mice, rats and guinea-pigs, 2 ml in rabbits, and 5 ml in dogs) with or without *B. pertussis* vaccine (80×10^6 organisms per ml—0·5 ml in rats, mice and guinea-pigs, 1 ml in rabbits, and 2·5 ml in dogs). Other groups of animals were injected with only the vaccine. Every 4 days after the injection of antigen or vaccine, samples of blood from the tail vein of rats and mice, the ear vein of guinea-pigs and rabbits, and the femoral vein of dogs were removed for sugar assay using the Folin-Wu method.

The results in Table 1 show that *B. pertussis* vaccine alone induced a hypoglycaemia of 25–35% which commenced about 8 days after treatment, reached a peak at about 12 days, and ended by about day 24. The pattern of events in each of the species was similar. When the antigen was given alone, a significant hypoglycaemia was found in rats, mice and guinea-pigs but not in rabbits and dogs. Whereas the blood sugar

Table 1. *Effect of* B. pertussis *vaccine (BPV) and horse serum on the blood sugar concentrations of animals at different times after treatment.* Mean values (mg/100 ml) from groups of 8 animals are recorded.

Species	Treatment	Day after treatment						
		0	4	8	12	16	20	24
Rat	BPV	102	88	78*	76*	78*	90	100
	Horse serum	104	108	108	92	88*	94	102
Mouse	BPV	98	90	82	78*	78*	86	98
	Horse serum	92	94	96	80	76*	78*	94
Guinea-pig	BPV	110	98	80*	82*	74*	92	100
	Horse serum	115	112	110	115	110	92	74*
Rabbit	BPV	115	88	80*	86*	88	98	100
	Horse serum	112	122	120	124	128	120	100
Dog	BPV	120	110	90	84*	92	108	102
	Horse serum	124	118	120	130	124	110	100

* Significantly different from control values ($P < 0.05$).