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Aromatic amino acetylation in the adult and neonatal marmoset

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Acetylation of sulphadiazine, sulphadimidine and *p*-aminobenzoic acid (PAB) was studied in the marmoset (*Callithrix jacchus*).

Sulphadiazine (100 mg/kg) was administered as a suspension in Cytacon. Unchanged dose and metabolites excreted in urine were identified by paper and high-pressure liquid chromatography and the relative amounts of free and acetylated drug determined (Bratton & Marshall, 1939). Radioactive components present in the urine excreted by 5 animals dosed with [^{35}S]-sulphadiazine were separated by paper chromatography and the distribution of the radioactivity measured by counting successive 1.0 cm strips cut from the chromatograms. Histograms constructed from these results showed that *N*-acetylsulphadiazine comprised 34.0% ($\pm$1.8 s.e. mean) and sulphadiazine 35.5% ($\pm$2.9 s.e. mean) of the radioactive components excreted. The extent to which the adult marmoset acetylates sulphadiazine thus resembles that (45%) reported for man (Uno & Sekine, 1966).

When sulphadimidine (45 mg/kg) was administered to 19 adult marmosets the average proportion of the drug excreted in the acetylated form was 69.9% ($\pm$1.3 s.e. mean) suggesting that the animals examined were 'fast acetylators'. This was confirmed by analysis (Weber & Brenner, 1974) of the free and acetylated sulphadimidine in blood samples taken at 4 and 6 h after administration of the dose.

PAB (100 mg/kg) was administered, in solution as the sodium salt, mixed with Cytacon, to adult marmosets and rats and mixed with milk to neonates. The results (Table 1), obtained by analysis (Davis & Yeary, 1977) of urine samples collected for 6 h after dosing suggest that enzymes catalysing the conjugation of PAB develop at different rates and that the PAB metabolic profiles finally developed in the two species are different. The results for the rat are in agreement with those reported by Brandt (1964, 1966). In contrast to the marmoset the extent of acetylation of PAB seen in the human infant, decreases with age (Vest, 1965; Vest & Salzberg, 1965)

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Table 1 Urinary excretion of *p*-aminobenzoic acid and its metabolites by marmosets and rats in 6 h after administration of dose (100 mg/kg). The results are expressed as average percentages ± s.e. mean; where only two animals were used the mean values ± difference from mean are given. N.D. = none detected; a = groups of four animals

Species	*Number of animals used*	*Age (days)*	*% dose excreted*	*Relative proportions of dose and metabolites in urine*				
				PAB	*PAAB*	*PAH*	*PAAH*	*PABG*
Marmoset	4	4 and 5	10	32.5 ± 4.5	46.0 ± 5.7	7.5 ± 1.5	N.D.	12.1 ± 3.7
	2	10 and 11	56.5 ± 5.5	4.55 ± 1.45	82.65 ± 1.75	3.6 ± 0.3	N.D.	9.6 ± 3.0
	3	Adult	57 ± 11.3	9.6 ± 4.5	67.5 ± 6.5	9.0 ± 2.1	1.7 ± 1.7	11.1 ± 3.9
Rat	3a	7	38.0 ± 9.1	N.D.	33.6 ± 1.0	32.8 ± 1.6	N.D.	33.6 ± 2.4
	3a	11	16 ± 3.8	N.D.	42.5 ± 1.4	56.7 ± 3.1	N.D.	6.8 ± 1.6
	2	Adult	86.5 ± 2.5	1.25 ± 1.25	17.8 ± 1.4	67.65 ± 1.75	5.85 ± 1.35	7.25 ± 0.55

PAB, *p*-aminobenzoic acid; PAAB, N-acetyl-*p*-aminobenzoic acid; PAH, *p*-aminohippuric acid; PAAH, N-acetyl-*p*-aminohippuric acid; PABG *p*-aminobenzoylglucuronide.

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Species variation in the taurine conjugation of clofibric acid

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Clofibric acid (4'-chlorophenoxyisobutyric acid) is the pharmacologically active metabolite of the hypolipidaemic agent, clofibrate, and is itself used as a hypolipidaemic. This acid is metabolised by glucuronic acid conjugation in rat (Cayen, Fernandini, Greselin, Robinson & Dvornik, 1977) and man (Houin & Tillement, 1978), and in dog gives rise to a second unknown conjugate (Cayen *et al.*, 1977). We now report a reinvestigation of the metabolism of clofibric acid in six animal species and man. The present study confirms that it forms its ester glucuronide *in vivo*, and shows for the first time its extensive conjugation with taurine in three carnivorous species.

[^{14}C]-Clofibric acid (100 mg/kg; 3 μCi/animal) was administered to rats, guinea pigs, rabbits, cats, dogs and ferrets by intraperitoneal injection dissolved in propane-1,2-diol and their urine collected for up to 3 days. Three healthy male volunteers took [^{14}C]-clofibric acid (500 mg; 1 μCi) by mouth in a hard gelatine capsule and collected their urine for 48 h. The [^{14}C] content of the urines was assayed by liquid scintillation counting, and urinary metabolites determined by solvent extraction, thin-layer chromatography, colour reactions and enzymic and chemical hydrolysis. Quantitative and qualitative results are given in Table 1. The cat, dog and ferret excreted the administered [^{14}C] slowly, with 24–39% of the dose excreted in 24 h and a total of 50–72% recovered in 3 days. Each species excreted as the major metabolite the taurine conjugate of clofibric acid, with smaller amounts of the unchanged acid and its ester glucuronide also present. The taurine conjugate was identified subsequent to its isolation, hydrolysis to clofibric acid and taurine, identified by chromatography as such and as its dansyl derivative, and by its infra red spectrum.

In the rat, rabbit, guinea-pig, mouse and man, at least 60% of the administered dose was recovered in the urine in 24 h, with further amounts excreted up to 3 days (total 66–96%). The only compounds present in the urines of these species were unchanged clofibric acid and its glucuronic acid conjugate. In each species, this was identified as the 1-*O*-acyl glucuronide by comparison of its chromatographic, solvent extraction and hydrolysis properties with a fully characterised sample of this metabolite isolated from rabbit urine (Caldwell & Emudianughe, 1979). Little is known about the chemical and biological factors

Table 1 The metabolism of clofibric acid in man and animals. Drug administration, urine collection and analysis as described in the text. Figures represent the means of at least three experiments

% [^{14}C]-dose in urine	Rat	Guinea Pig	Rabbit	Dog	Cat	Ferret	Man
0–24 h	95.6	73.6	60.4	38.9	23.7	24.0	59.8
0–72 h	—*	—*	73.9	66.4	50.0	71.8	80.0
%0–24 h urinary [^{14}C] *present as*							
Free acid	44	20	9	30	56	23	5
Glucuronide	56	80	91	19	tr	5	95
Taurine Conjugate	n.d.	n.d.	n.d.	51	43	72	n.d.

* 24 h collection only. tr = trace. n.d. = not detected.