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Effects of monoamine oxidase inhibitor (MAOI) pretreatment on the fate of intraduodenally instilled [^{14}C]-tyramine

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Dietary tyramine can precipitate migraine (Hanington, 1967) and hypertensive crises in subjects treated with MAOI (Blackwell, Marley, Price & Taylor, 1967). Since (±)-deprenyl, a MAO B inhibitor, is reputedly free of hypertensive complications (Varga & Tringer, 1967) the fate in cats of intraduodenally instilled [^{14}C]-tyramine and the effect thereon of MAOI was investigated as was the influence of histamine, which can occur in the same foods as tyramine (Marley & Blackwell, 1970).

Following intraduodenal instillation of [^{14}C]-tyramine, blood samples were removed from the portal vein (PV) and cranial mesenteric artery (CMA) and chromatographed (Tacker, McIsaac & Creaven, 1970), the separated [^{14}C] compounds being measured by scintillation spectrometry. The principal [^{14}C] compound recovered from the PV in control experiments (Table 1) was *p*-hydroxyphenylacetic acid (pHPA), although tyramine was absorbed and accounted for progressively larger proportions of the total radioactivity as the dose increased. Absorption of tyramine following small intraduodenal doses has not been previously noted, possibly because of the limits imposed by bioassay techniques. Other metabolites (octopamine, tyramine sulphate, methyl tyramine and tyrosol) together constituted not more than 17%

Table 1 [^{14}C]-Tyramine (TYR) and p-hydroxyphenylacetic (pHPA) acid in portal venous (PV) and cranial mesenteric arterial (CMA) blood for control cats and those pretreated with MAOI

		[^{14}C]-Tyramine; 5 μCi with 1.7 μmol/kg			8.5 μmol/kg			17 μmol/kg		
		TYR	pHPA	n	TYR	pHPA	n	TYR	pHPA	n
		pmol/ml								
Control	PV	132	1259	4	1980	4470	3	6633	17,506	3
	CMA	42	462	4	350	2710	3	1421	12,290	3
Clorgyline	PV	838	520	3	6059	2590	3	9590	5327	3
(24.5 μmol/kg)	CMA	496	468		1694	2875		3984	2093	
Deprenyl	PV	104	584	3	2326	4833	3	7485	13,868	3
(4.5 μmol/kg)	CMA	49	487		424	2390		1249	7530	
Mebanazine	PV	752	516	2						
(10 μmol/kg)	CMA	325	414							
(40 μmol/kg)	PV	1584	168	2						
	CMA	1074	100							
Tranylcypromine	PV	1099	407	2						
(2.8 μmol/kg)	CMA	616	366							
(14 μmol/kg)	PV	1474	173	2						
	CMA	1193	213							
Nialamide	PV	2100	206	2						
(80 μmol/kg)	CMA	1193	194							
Histamine	PV	405	2101	3	3201	6435	3	6279	16,640	3
(5 μmol/kg)	CMA	168	1063		621	3666		859	9119	

Values are mean results of serial determinations (approximately 15 per experiment) from *n* experiments.

of the total radioactivity recovered, and were not enhanced when MAO was inhibited. The percentage of tyramine in CMA blood was between 17.6% and 31.8% of that found in PV blood, while the corresponding values for pHPA were 36.6% and 76.9% suggesting selective removal/metabolism of tyramine in the circulation, particularly with the larger doses. The presence of tyramine in mesenteric arterial blood (Table 1) meant that the liver, heart and lungs failed to completely remove or inactivate the amine.

When histamine (5.0 μmol/kg) was additionally instilled with tyramine, enhanced amounts of tyramine appeared in PV and CMA blood with 1.7 and 8.5 μmol/kg doses (tyramine) but not with the larger dose, suggesting that absorption and metabolism of tyramine are dependent on the relative concentrations of other amines.

The effect of non-selective MAOI instilled 90 min prior to instillation of tyramine was to enhance in a dose-dependent manner the amount of tyramine in PV and CMA blood, tranylcypromine being particularly effective (Table 1). Following clorgyline, a selective MAO A inhibitor, tyramine was absorbed in amounts comparable to those with mebanazine, 10 μmol/kg, (see Table). In contrast and an explanation for Varga & Tringer's 1967 findings the amount of absorbed tyramine following an MAO B inhibitor, (−)-deprenyl, was similar to that in control cats, although MAO activity *in vitro* (Imrie, Marley & Thomas, 1979) was inconsistent with the *in vivo* results.

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Inhibition of synaptosome ATPase by PGE_1 may be dependent on a soluble factor

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The inhibition by PGE_1 of a sodium-activated, magnesium-dependent adenosine triphosphatase (Na^+-ATPase) prepared from CNS nerve terminals (Gilbert & Wyllie, 1975) has been examined in more detail.

Experiments have shown that while inhibition of Na^+-ATPase by PGE_1 occurs in synaptosomes which have been prepared intact and subsequently ruptured in the ATPase assay medium, this was not the case when the synaptosomes were stabilized in the medium by the addition of sucrose to increase the osmolarity. (Table 1).

From these and other studies it has been found that increasing the medium osmolarity in the range 355–450 m osmol/l represents a change from a large to a small percentage of ruptured synaptosomes. The osmolarity-dependent diminution of Na^+-ATPase in-

Table 1 % inhibition of synaptosome Na^+-ATPase by PGE_1*

	Medium Osmolarity (m osmol/l)				
	355	375	400	425	450
Fresh	70.5 ± 3.0 (6)	66.7 ± 6.5 (3)	39.1 ± 8.8 (4)	8.0 ± 5.6 (3)	9.2 ± 9.1 (6)
Rethawed	71.2 ± 5.1 (3)	72.4 ± 3.1 (3)	69.8 ± 6.2 (4)		73.7 ± 5.5 (4)

* 10 μg/ml control activity 3.4 ± 0.3 (6) μmol $mgPr^{-1}$ h^{-1} corresponding to 0% inhibition.