drawn from the right. Endogenous NA release was blocked by i.v. infusion of pentolinium (0.02 mg kg^{-1} min^{-1}). NA was infused (a) without blockade (b) with blockade of all 4 pathways (c) individual blockade of each pathway.

In (a) NA clearance was 69.37 ± 5.7 ml kg^{-1} min^{-1}. In (b), it was reduced to 15.9 ± 2.1 ml kg^{-1} min^{-1} ($P < 0.001$). In (c), it was reduced by Up_1 blockade to 42.46 ± 4.8 ml kg^{-1} min^{-1} ($P < 0.01$), by COMT blockade to 52 ± 6.3 ml kg^{-1} min^{-1} ($P < 0.01$) and by Up_2 blockade to 59 ± 5.3 ml kg^{-1} min^{-1} ($P < 0.05$). In (a) the elimination of NA after cessation of the infusion appears to be described by a multiexponential function, with a late phase elimination constant of 0.048 min^{-1}. This is not seen after Up_1 blockade, in (b).

Up_1 and COMT appear to be the major pathways in the clearance of infused NA. Some of the NA cleared by Up_1 may be later re-released into the circulation.

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Effect of penicillamine, hydrallazine and phenelzine on the function of pyridoxal-5'-phosphate

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The effect of a number of drugs on vitamin B_6 metabolism has been studied in Lister Hooded rats. Abnormal metabolism was detected by an increased urinary excretion of xanthurenic acid after an oral loading dose of L-tryptophan, a commonly used method of detecting vitamin B_6 deficiency (Sauberlich, *et al.*, 1972), and by measuring liver pyridoxal-5'-phosphate (PLP) content.

Xanthurenic acid excretion was increased, relative to the pretreatment levels, after 14 days' treatment with DL-penicillamine (435% increase), hydrallazine (348% increase) and phenelzine (342% increase). Concurrent treatment with drug and pyridoxine hydrochloride reversed these increases almost completely. However, the liver PLP content was decreased only in the DL-penicillamine-treated rats.

Penicillamine, hydrallazine and phenelzine all react with PLP *in vitro*. However, it has been shown in studies with cycloserine and isonicotinic acid hydrazide that interaction between drug and coenzyme, and excretion of the resulting product from the body, may not be the main mechanism of antagonism of PLP function (Rosen, Mihich, & Nichol, 1964; Krishnamurthy, *et al.*, 1967). Experiments were carried out to determine whether hydrallazine and phenelzine inhibited a PLP-dependent stage in tryptophan metabolism.

The action of penicillamine, hydrallazine and phenelzine on a partially-purified preparation of rat kidney kynurenine aminotransferase (KAT), a PLP-dependent enzyme (Mason, 1957), was investigated using the method of Kilgallon & Shepherd (1977). DL-penicillamine did not inhibit KAT, whilst hydrallazine and phenelzine showed non-competitive inhibition with respect to substrate with K_i values of 1.06×10^{-4} M and 5.07×10^{-5} M respectively. These results agree with those recently reported by Allegri Costa & De Antoni (1979) for the action of D-cycloserine, which also reacts with PLP, on KAT. When the PLP concentration was increased, the inhibition due to phenelzine increased. It is suggested that the hydrazone formed between phenelzine and PLP is a more potent inhibitor of KAT than is phenelzine itself.

Penicillamine, hydrallazine and phenelzine affect the normal functioning of PLP. Hydrallazine and phenelzine inhibit KAT, a PLP-dependent enzyme, whilst penicillamine lowers liver PLP levels, perhaps by an effect on the PLP-producing enzymes, pyridoxal kinase or pyridoxal phosphate oxidase.

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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.