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Effect of some monoamine oxidase inhibitors on the thiamin status of rabbits

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1 The monamine oxidase (MAO) inhibitors harmaline, tranylcypromine, deprenyl, clorgyline and iproniazid were injected intraperitoneally for five days to rabbits at doses that produced significant MAO inhibition. The first three inhibitors raised the concentrations of pyruvate and lactate in blood, decreased the activity of erythrocyte transketolase (TK) and increased the thiamin pyrophosphate (TPP) effect. The drugs also produced anorexia and loss of body weight. The changes were suggestive of an adverse effect on the thiamin status. Clorgyline and iproniazid, however, raised the blood concentrations of pyruvate and lactate but did not affect significantly erythrocyte TK activity or TPP effect.

2 Treatment of rabbits for 14 days with the thiamin antagonists pyrithiamin ($20\,\mu g\,kg^{-1}$) or oxythiamin ($0.8\,mg\,kg^{-1}$) produced a significant drop in TK activity and increase in the lactate and pyruvate concentrations as well as an increase in TPP effect. Pyrithiamin (5, 10 or $20\,\mu g\,kg^{-1}$, 14 days) lowered significantly the activity of MAO in the liver and brain of rabbits. Treatment with the other antagonist, oxythiamin, at doses of 0.2 or $0.4\,mg\,kg^{-1}$ for 14 days had no significant effect on MAO activity. At a dose of $0.8\,mg\,kg^{-1}$ a significant drop in MAO activity occurred.

3 A pair-feeding trial indicated that the biochemical changes produced in animals treated with MAO inhibitors were attributable to the drugs *per se*, and not to the ensuing anorexia.

4 Thiamin ($100\,\mu g\,kg^{-1}$, subcutaneously) when given concomitantly with pyrithiamin, oxythiamin, harmaline, deprenyl and tranylcypromine was effective in preventing the development of thiamin deficiency.

Introduction

It is known that several nutritional factors affect the activity of monoamine oxidase (MAO) (monoamine: O_2 oxidoreductase (deaminating) EC 1.4.3.4.). For example, iron deficiency anaemia was found to be associated with a marked reduction in platelet MAO activity (Callender *et al.*, 1974) and alterations in the intake of riboflavin can also affect activity of platelet MAO activity (Murphy, 1976). However, the relationship between MAO activity and the thiamin status of animals is largely unknown. Some conditions treated in man by the administration of MAO inhibitors, e.g. depression, and other conditions (e.g. alcoholism), adversely affect the thiamin status (Wood *et al.*, 1977; Connor, 1981). In view of the wide clinical use of MAO inhibitors (Pare, 1976; 1979), it was thought of interest to investigate the effect of five different MAO inhibitors on the thiamin status of rabbits.

The activity of MAO has been shown to be increased, and 5-hydroxytryptamine (5-HT) decreased, in the brain and small intestine of thiamin-deficient rats (Gal & Drewes, 1961; Meltzer, 1961). This finding is at variance with reports from Japan, which indicated that thiamin deficiency induces MAO inhibition, and moreover, produces a significant increase in monoamine concentrations in the tissues of treated rats (Iwata *et al.*, 1969; Iwata, 1976). This apparent discrepancy led to the investigation in the present experiments of the effect of two thiamin antagonists (oxythiamin and pyrithiamin) on the activity of MAO.

Methods

Animals

Experiments were carried out in clinically healthy male rabbits (local type), weighing about 1.5 to 2 kg, and kept either individually, or as groups of five. Except where mentioned, food (fresh green lucerne and sorghum grains) and water were provided *ad libitum*.

Blood was collected by cardiac puncture, using heparinized syringes fitted with 21 G needles, into chilled pre-weighed tubes and spun down at 900 *g* for 20 min to separate plasma.

Thiamin status

This was assessed by determining spectrophotometrically the blood concentrations of lactate and pyruvate (Marbach & Weil, 1967), erythrocyte transketolase (TK) activity, and the percentage thiamin pyrophosphate (TPP) effect (Brin, 1974). The TPP effect, which refers to the increase in TK activity in a deficient haemolysate due to the addition of TPP before incubation expressed as % of that in a deficient haemolysate without the addition of TPP, was obtained from the expression:

$$\text{TPP effect (\%)} = \frac{\text{(Test with TPP)} - \text{(Test without TPP)}}{\text{(Test without TPP)}} \times 100$$

Body weight and food intake were measured daily.

Pair-feeding

To find out whether the effects produced were due to the drugs themselves, or were the result of anorexia, a pair-feeding technique described previously (Ali & Bartlet, 1982) was employed. Rabbits were caged individually. Some rabbits were fed *ad libitum* and given harmaline, deprenyl or tranylcypromine by intraperitoneal injection, or injected with the vehicle only (controls). The values obtained for food intake was subsequently used for pair-feeding. The pair-fed animals were given amounts of food which were equivalent to those consumed by the controls and drug-treated animals.

MAO inhibitors

Five chemically unrelated MAO inhibitors were used. The stock solutions of these drugs were prepared in distilled water (1% w/v) and diluted as required with 0.9% w/v NaCl solution before use. Doses refer to the base. Clorgyline (M & B) was given at a dose of 20 mg kg^{-1}, harmaline (Sigma) at 5 mg kg^{-1}, iproniazid (Sigma) at 50 mg kg^{-1}, (−)-deprenyl (Prof. Knoll, Hungary) at a dose of 10 mg kg^{-1}, and tranylcypromine (S.K. & F) at a dose of 10 mg kg^{-1}. All the drugs were injected intraperitoneally for 5 consecutive days at a dose volume of 1 ml kg^{-1}.

Effects of thiamin antagonists on MAO activity

In this experiment pyrithiamin and oxythiamin were injected subcutaneously for 14 days to rabbits at doses which are known to antagonize thiamin in rats (Bai *et al.*, 1971), and MAO activities in the liver and brain measured.

Thiamin administration

Thiamin was given in emulsion form with sesame oil and Trifox X-45, and injected subcutaneously at a dose of 100 μg kg^{-1}.

Determination of MAO activity

Rabbits were killed by stunning followed by decapitation, and the liver and brain quickly removed and homogenized in 0.5 M phosphate buffer for the spectrophotometric determination of MAO activity by the method of Weissbach *et al.* (1960), which depends on the disappearance of kynuramine.

Statistical analysis

Values presented are means ± s.e.means (number of observations). Student's *t* test was used to test the significance of differences between the means and these were considered significant when *P* values were less than 0.05.

Table 1 The effect of monoamine oxidase (MAO) inhibitors on the enzyme activities in liver and brain of rabbits

	MAO activity (μmol kynuramine h^{-1} g^{-1} tissue)	
	Liver	*Brain*
Control	8.3 ± 0.6 (5)	5.3 ± 0.5 (5)
Iproniazid (50 mg kg^{-1})	0.5 ± 0.1 (5)**	0.4 ± 0.1 (5)**
Harmaline (5 mg kg^{-1})	0.8 ± 0.1 (5)**	0.5 ± 0.1 (5)**
Tranylcypromine (10 mg kg^{-1})	1.3 ± 0.2 (5)*	2.1 ± 0.2 (5)*
Deprenyl (10 mg kg^{-1})	1.6 ± 0.2 (5)*	0.6 ± 0.1 (5)**
Clorgyline (20 mg kg^{-1})	0.9 ± 1.0 (5)*	0.5 ± 0.1 (5)**

Values shown are means ± s.e.mean of the number of animals in parentheses. Animals were killed 5 days after treatment.
*$P < 0.05$, **$P < 0.01$, compared with the control.

Drugs and chemicals

The following drugs were used: anthrone (Sigma), clorgyline (M & B), deprenyl (Prof. Knoll, Hungary), glycine (B.D.H., biochemical grade), harmaline (Sigma), heparin sodium (Sigma), kynuramine dihydrobromide (Sigma), (+)-lactic acid (Sigma), lactic dehydrogenase (type 3; Sigma), metaphosphoric acid (B.D.H.), nicotinamide adenine dinucleotide (oxidized and reduced forms; Sigma), oxythiamin (Sigma), ribose-5-phosphate monobarium salt (Sigma), pyrithiamin (Sigma), sodium pyruvate (Sigma), thiamin HCl (Sigma), thiamin pyrophosphate Cl (Sigma), thiourea (Aldrich), tranylcypromine (S.K.F.), and Triton X-45 (Sigma). Any other chemicals used were of Analytical Reagent grade.

Results

Effects of drugs on monoamine oxidase

The five MAO inhibitors produced about 80 to 100% inhibition of MAO ($P < 0.01$). As shown in Figure 1, MAO activities in the liver and brain of the pyrithiamin-treated rabbits were significantly lower ($P < 0.05$), than those of the control at the three doses used. No significant change, however, was found in the enzyme activities of the oxythiamin-treated animals ($P > 0.1$) at doses of 0.2 and 0.4 mg kg^{-1}. At a dose of 0.8 mg kg^{-1} a significant drop ($P < 0.05$) was observed.

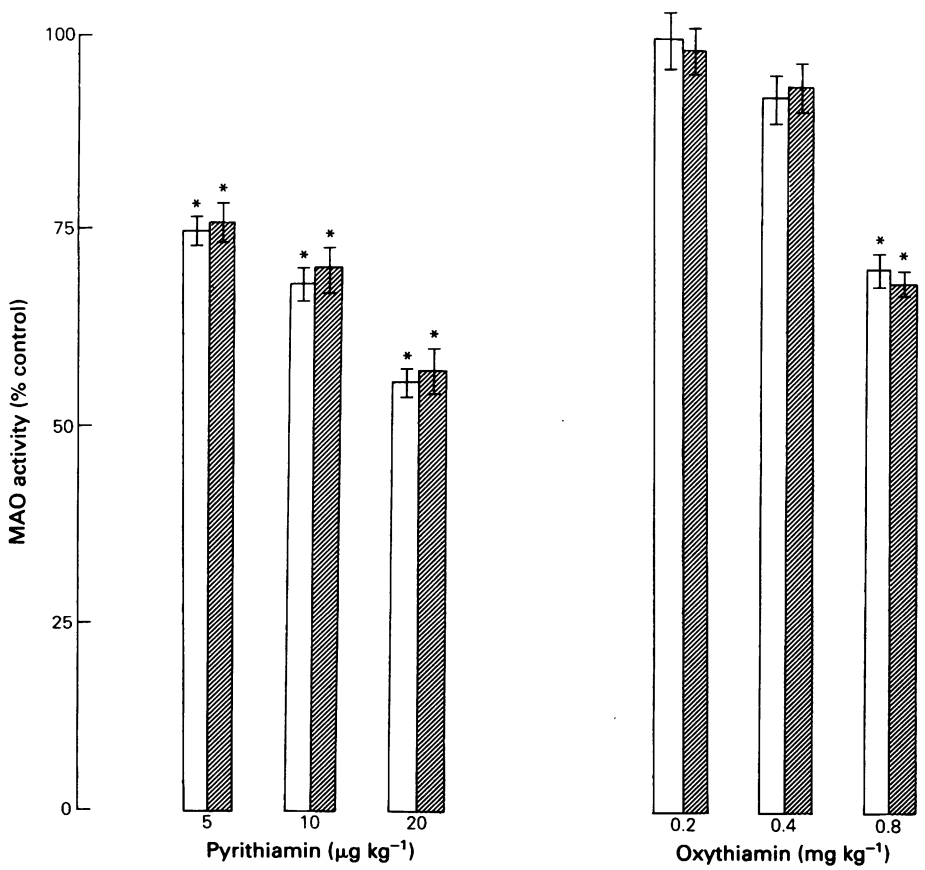

Figure 1 Monoamine oxidase (MAO) activities in liver (open columns) and brain (hatched columns) of rabbits treated with pyrithiamin (5, 10 and 20 μg kg^{-1} for 14 days) and oxythiamin (0.2, 0.4 and 0.8 mg kg^{-1} for 14 days). Each column and vertical bar depict the mean and s.e.means of 4 animals. Asterisks denote a significant difference ($P < 0.05$) from the control.

Effect of MAO inhibitors on food intake and growth

Harmaline, deprenyl and tranylcypromine produced about a 20% reduction in the food intake of rabbits, and about a 12% reduction in growth, as compared with the controls.

Iproniazid and clorgyline did not affect food intake or growth markedly. No obvious clinical changes were observed in any of the treated animals.

Effect of MAO inhibitors and thiamin antagonists on biochemical indices of thiamin status

The results of this experiment are shown in Table 2. The concentrations of lactate and pyruvate in the blood were significantly increased in all the treated rabbits ($P<0.05$). However, TK activity was significantly decreased ($P<0.05$) and TPP effect increased ($P<0.01$) only in rabbits treated with harmaline, deprenyl or tranylcypromine.

Indices of thiamin status in pair-fed animals

Harmaline, deprenyl or tranylcypromine reduced food intake and growth of rabbits. To differentiate between the effects of these drugs *per se* on the thiamin status, and those caused by reduced food intake and growth, the rabbits were individually housed and treated with these three MAO inhibitors, and the same indices of thiamin status measured as before. Data obtained from this experiment were compared with those obtained from untreated rabbits pair-fed with treated animals. The results of this experiment (Table 3) indicated that the pair-fed animals had significantly lower lactate and pyruvate concentrations, higher TK activity, and lower TTP effect, indicating that the effects produced were attributable to the drugs *per se* and not to the ensuing anorexia.

Effect of thiamin administration on thiamin status of rabbits treated with MAO inhibitors and thiamin antagonists

In a single experiment thiamin 100 $\mu g\,kg^{-1}$ as an oil emulsion was given subcutaneously, concomitantly with oxythiamin (0.8 $mg\,kg^{-1}$, 14 days), pyrithiamin (20 $\mu g\,kg^{-1}$, 14 days), harmaline (5 $mg\,kg^{-1}$, 5 days), deprenyl (10 $mg\,kg^{-1}$, 5 days) or tranylcypromine (10 $mg\,kg^{-1}$, 5 days). The results of this experiment are shown in Table 4. Thiamin treatment caused a significant decrease in the concentrations of lactate and pyruvate in blood, and the TPP effect, and a significant increase in the TK activity, of all treated animals. No significant difference between the control and the thiamin-treated rabbits ($P>0.1$) was found.

Table 2 The effect of monoamine oxidase (MAO) inhibitors, pyrithiamin and oxythiamin on some indices of thiamin status in rabbits

	Blood lactate (mM)	*Blood pyruvate* (mM)	*Transketolase activity in erythrocytes* ($u\,l^{-1}$)	*Thiamin pyrophosphate effect* (%)
Control	1.34 ± 0.11 (5)	0.06 ± 0.004 (5)	62.01 ± 5.31 (5)	3.81 ± 0.21 (5)
Iproniazid (50 $mg\,kg^{-1}$, 5 days)	3.20 ± 0.30 (5)*	0.22 ± 0.011 (5)*	52.39 ± 6.21 (5)	6.87 ± 0.82 (5)
Harmaline (5 $mg\,kg^{-1}$, 5 days)	3.99 ± 0.42 (5)*	0.28 ± 0.021 (5)*	39.81 ± 5.11 (5)*	19.33 ± 6.22 (5)**
Tranylcypromine (10 $mg\,kg^{-1}$, 5 days)	4.02 ± 0.44 (5)**	0.27 ± 0.023 (5)**	43.99 ± 4.90 (5)*	19.33 ± 6.22 (5)**
Deprenyl (10 $mg\,kg^{-1}$, 5 days)	3.28 ± 0.31 (5)*	0.25 ± 0.020 (5)*	41.81 ± 4.93 (5)	21.81 ± 6.20 (5)**
Clorgyline (20 $mg\,kg^{-1}$, 5 days)	4.10 ± 0.43 (5)*	0.23 ± 0.022 (5)*	55.31 ± 7.30 (5)	7.21 ± 0.82 (5)
Pyrithiamin (20 $\mu g\,kg^{-1}$, 14 days)	4.20 ± 0.44 (4)**	0.24 ± 0.027 (4)*	30.32 ± 7.11 (4)*	29.31 ± 2.1 (4)**
Oxythiamin (0.8 $mg\,kg^{-1}$, 14 days)	4.11 ± 0.50 (4)*	0.25 ± 0.027 (4)*	40.34 ± 3.81 (4)*	23.31 ± 2.2 (4)**

The values shown are means ± s.e.mean of the number of animals in parentheses. MAO inhibitors were injected i.p., and the thiamin antagonists s.c.
*$P<0.05$, **$P<0.01$, compared with the controls.

Table 3 Some indices of thiamin status in rabbits treated with harmaline, deprenyl or tranylcypromine, and pair-fed counterparts

	Blood lactate (mM)	*Blood pyruvate* (mM)	*Transketolase activity in erythrocytes* ($u\,l^{-1}$)	*Thiamin pyrophosphate effect* (%)
Harmaline ($5\,mg\,kg^{-1}$)	4.22 ± 0.41 (4)	0.27 ± 0.02 (4)	39.77 ± 4.21 (4)	18.77 ± 2.1 (4)
Pair-fed	1.38 ± 0.20 (4)	0.07 ± 0.011 (4)	60.11 ± 5.71 (4)	3.71 ± 0.31 (4)
$P <$	0.05	0.05	0.05	0.01
Deprenyl ($10\,mg\,kg^{-1}$)	3.24 ± 0.38 (4)	0.23 ± 0.02 (4)	42.72 ± 4.11 (4)	22.37 ± 2.3 (4)
Pair-fed	1.48 ± 0.21 (4)	0.06 ± 0.012 (4)	63.33 ± 6.81 (4)	4.41 ± 0.37 (4)
$P <$	0.05	0.05	0.05	0.01
Tranylcypromine ($10\,mg\,kg^{-1}$)	4.00 ± 0.39 (4)	0.25 ± 0.31 (4)	44.33 ± 3.21 (4)	19.81 ± 2.11 (4)
Pair-fed	1.33 ± 0.20 (4)	0.07 ± 0.011 (4)	68.31 ± 9.31 (4)	3.81 ± 0.41 (4)
$P <$	0.05	0.05	0.05	0.01

The values shown are means ± s.e.mean of the number of animals in parentheses. The drugs were injected i.p. for 5 days.

Discussion

The present experiments showed that treatment of rabbits with harmaline, deprenyl or tranylcypromine, at doses that caused significant inhibition of MAO activity, reduced food intake and growth of animals, and produced biochemical changes indicative of an adverse effect on the thiamin status of the treated rabbits. Iproniazid and clorgyline, however, only raised the blood concentrations of lactate and pyruvate, but did not affect significantly the TK activity or the TPP effect. Thus their effect on the thiamin status seems less certain. These results suggest that MAO inhibitors could affect adversely the thiamin status of treated subjects. This is particularly relevant in cases where there is a possibility of a

Table 4 The effect of thiamin administration on some indices of thiamin status in rabbits treated with harmaline, deprenyl, tranylcypromine, pyrithiamin or oxythiamin

	Blood lactate (mM)	*Blood pyruvate* (mM)	*Transketolase activity* (ul^{-1})	*Thiamin pyrophosphate effect* (%)
Control	1.34 ± 0.11 (5)	0.06 ± 0.004 (5)	62.21 ± 5.31 (5)	3.8 ± 0.21 (5)
Control + thiamin	1.21 ± 0.11 (3)	0.07 ± 0.005 (3)	63.31 ± 6.32 (3)	3.0 ± 0.31 (3)
Harmaline	4.22 ± 0.41 (4)	0.27 ± 0.02 (4)	39.77 ± 4.21 (4)	18.77 ± 2.1 (4)
Harmaline + thiamin	1.83 ± 0.12 (3)*	0.08 ± 0.009 (3)*	54.21 ± 5.90 (3)*	5.31 ± 0.6 (3)*
Deprenyl	3.24 ± 0.38 (4)	0.23 ± 0.02 (4)	42.72 ± 4.11 (4)	22.37 ± 2.3 (4)
Deprenyl + thiamin	2.00 ± 0.21 (3)*	0.10 ± 0.01 (3)*	59.31 ± 6.91 (3)*	6.91 ± 0.81 (3)*
Tranylcypromine	4.00 ± 0.39 (4)	0.25 ± 0.03 (4)	44.33 ± 3.41 (4)	19.81 ± 2.11 (4)
Tranylcypromine + thiamin	2.01 ± 0.42 (3)	0.11 ± 0.01 (3)	60.31 ± 6.21 (3)*	7.81 ± 0.71 (3)*
Pyrithiamin	4.20 ± 0.44 (4)	0.24 ± 0.25 (4)	39.32 ± 7.11 (4)	29.31 ± 2.1 (4)
Pyrithiamin + thiamin	2.13 ± 0.20 (3)	0.11 ± 0.03 (3)	63.39 ± 7.21 (3)*	8.01 ± 0.81 (3)*
Oxythiamin	4.11 ± 0.50 (4)	0.25 ± 0.027 (4)	40.34 ± 5.81 (4)	23.31 ± 2.2 (4)
Oxythiamin + thiamin	1.91 ± 0.20 (3)	0.12 ± 0.01 (3)	65.33 ± 6.3 (3)*	8.31 ± 0.59 (3)*

The values shown are means ± s.e.mean of the number of animals in parentheses. Thiamin was injected subcutaneously in an oil emulsion, at a dose of $100\,\mu g\,kg^{-1}$.
*$P < 0.05$, compared with the respective initial treatment.

deficiency in vitamins (such as in alcoholism). A more extensive study of the effect of MAO inhibitors on the thiamin status of humans seems justified.

Because of the anorexia caused by some MAO inhibitors, a pair-feeding experiment was undertaken to differentiate between the effects produced by the drugs *per se* and those produced secondarily as a result of reduced food intake and growth. The importance of pair-feeding in such experiments cannot be over emphasized (see e.g Sauer *et al.*, 1975; Ali & Bartlet, 1982). Pair-feeding indicated that the effects produced by the MAO inhibitors used were attributable to the drugs themselves and not secondary to the anorexia produced.

Thiamin status can be determined by biological or chemical methods. In the present work thiamin status was assessed by measuring the food intake and growth and several indices in the blood. The realiability of these indices has been confirmed by many authors previously (Wood *et al.*, 1977; Boni *et al.*, 1980; Lonsdale & Shamberger, 1980; Ali & Bartlet, 1982). In the present experiments no overt clinical changes (apart from anorexia) were observed in any of the treated rabbits. It is known that, in some cases, the chemical indices might suggest thiamin deficiency before the manifestation of obvious clinical signs of vitamin deficiency (Brin *et al.*, 1958).

Treatment with MAO inhibitors is known to increase pyruvic and lactic acid in rat blood (Gey & Pletscher, 1961). It was proposed that the rise was due to the fact that MAO inhibitors enhance glycolysis, and that this is related to an alteration of monoamine metabolism. The determination of blood lactate and pyruvate alone, however, may not be of any use in detecting marginal deficiencies of thiamin since blood lactate and pyruvate can be affected by many factors (Thompson, 1967).

Thiamin, given subcutaneously in an emulsion form to prolong its action, was effective in antagonizing the effects of pyrithiamin, oxythiamin and MAO inhibitors, on the thiamin status of rabbits. This suggested that the effect on thiamin status is readily reversible. The finding that thiamin injection did not affect the thiamin status of the control rabbits indicated that the diet of these animals contained adequate amounts of this vitamin.

The finding of Gal & Drewes (1961) that in thiamin-deficient rats the MAO activity in the brain and intestine is increased has been confirmed by Meltzer (1961), who also proposed that thiamin, or a metabolite thereof, is a MAO inhibitor. This result contradicts that of Iwata *et al.* (1969) who found that thiamin deficiency inhibited MAO activity. Although it could not be concluded from the present experiments whether 'natural' thiamin deficiency affects MAO activity, our results indicate that treatment with pyrithiamin produces a small but significant drop in the activity of MAO, while oxythiamin has no effect on the enzyme activity in liver or brain except when used at a rather high dose. The relationship between the mode of action of a MAO antagonist and the inhibition of MAO activity is not clear. It would be of interest to measure the enzyme activity and/or monoamine concentrations in animals raised on a thiamin-deficient diet.

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