Table 1. Alteration of convulsive responses to PTZ and 3-MP by prior administration of MSO

Convulsant	Without MSO*		After MSO†		Potency ratio
	N‡	CD_{50}§	N‡	CD_{50}§	
PTZ	38	43.1 (38.9–47.7)	24	35.9 (33.6–38.4)	1.21 (1.03–1.42)
3-MP	40	36.3 (33.9–38.8)	28	16.7 (14.9–18.7)	2.17 (1.91–2.46)

* Control data from Stone [12].

† MSO (300 mg/kg, i.p.) was given 165 min prior to injection of the convulsant.

‡ Number of mice.

§ The CD_{50} values are in mg/kg, i.p.; 95% confidence limits are given in parentheses.

was 241 ± 22 min. Of fourteen control animals given the same dose of MSO but no pyridoxal phosphate, ten had seizures within 5 hr, with a latent period of 246 ± 28 min. It is clear that the administration of pyridoxal phosphate had no protective effect; hence, the action of MSO probably is not on the coenzyme or its formation.

In summary, MSO is found to potentiate the convulsive response of mice to 3-MP (which inhibits GAD activity) to a much greater extent than it potentiates the response to PTZ (which is not thought to act via the GABA system). This resembles an effect of known GAD inhibitors, and adds support to the hypothesis that MSO induces excitation through an action on GABA metabolism. Since injected pryidoxal phosphate does not protect against MSO-induced seizures, an effect of MSO on the synthesis or activity of the coenzyme seems improbable.

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Increase of cardiac taurine by glucocorticoids

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A high concentration of taurine is present in mammalian heart [1], and taurine also has been reported to have pharmacological effects on the heart [2–8]. However, the physiological function of taurine in the heart is unknown, although it has been suggested that taurine may serve as an electrolyte modulator [9–11].

Previously, we [12] studied the effects of various factors and drugs on cardiac taurine content, and found that reserpine increased the taurine content significantly. Later, we found that this effect involved adrenocortical function (unpublished observations). These findings suggest that the metabolism of taurine in the heart may be regulated by adrenocortical hormones. In this work, we examined the effects of various steroid hormones on the taurine content in the heart to obtain more information on the relation between endocrine function and the metabolism of taurine in the heart. We also examined whether the effect of the hormones on taurine content is related to blood pressure, in view of the report [13] that its content increases in hypertensive rats. The present study shows that taurine content in the heart is increased by chronic administration of glucocorticoids, but not of other steroid hormones, and that the increases are accompanied by high blood pressures.

Male Sprague–Dawley rats, weighing 110–160 g, were used throughout. Cortisone acetate (as a suspension in physiological saline) and other hormones (as suspensions in sesame oil) were injected subcutaneously once a day for the indicated period.

We found that the taurine content in the heart showed a circadian rhythm (unpublished observations), and so the rats were decapitated at 10:00 a.m. to avoid variations due to this rhythm. Taurine was determined as described previously [12, 14, 15]. Systolic blood pressures of rats were measured indirectly using a Programmed Electro-Sphygmo-

Table 1. Effects of various steroid hormones on the taurine content in the heart*

	Dose (mg/kg)	N	Body wt (g) Initial	Body wt (g) Final	Heart wt (g)	Taurine content (μmoles/g wet wt)
Expt. 1						
Saline (control)		5	153 ± 3	226 ± 9	0.79 ± 0.04	20.2 ± 1.6
Cortisone acetate	20	5	151 ± 3	169 ± 5†	0.70 ± 0.02	28.2 ± 1.4‡
Expt. 2						
Sesame oil (control)		5	115 ± 1	168 ± 5	0.62 ± 0.02	20.6 ± 0.4
Hydrocortisone acetate	20	5	125 ± 2	122 ± 2†	0.58 ± 0.01	28.6 ± 0.5†
Prednisone	8	4	122 ± 2	147 ± 3†	0.61 ± 0.03	23.2 ± 0.6‡
Expt. 3						
Sesame oil (control)		6	141 ± 3	196 ± 4	0.76 ± 0.02	21.4 ± 0.9
17β-Estradiol	7	6	140 ± 2	138 ± 5†	0.55 ± 0.02†	21.0 ± 1.6
Testosterone propionate	20	5	136 ± 2	196 ± 4	0.74 ± 0.02	23.6 ± 1.5
Deoxycorticosterone	20	6	135 ± 2	185 ± 4	0.69 ± 0.02	23.2 ± 1.8

* Hormones were administered for 7 days. Values are expressed as means ± S. E. N = number of animals.
† $P < 0.01$, compared with the control value (Student's t-test).
‡ $P < 0.05$, compared with the control value (Student's t-test).

manometer PE-300 (NARCO BIO-SYSTEM INC.).

The taurine content in the heart increased on prolonged administration of glucocorticoids (for 7 days), such as cortisone acetate, hydrocortisone acetate and prednisone (Table 1, Expts. 1 and 2). The increases due to the glucocorticoids were also significant when the taurine content was expressed as total taurine content per heart (data not shown), since glucocorticoids did not affect the heart weight. No significant change in the taurine content was found in rats treated with other steroid hormones (Table 1, Expt. 3). Hydrocortisone acetate (20 mg/kg) for 2, 3, 4 and 5 days also increased the taurine content (Table 2). But, a single injection did not affect the cardiac taurine content. Furthermore, this effect was still observed at lower concentrations of drug (Table 2).

Table 2. Effect of hydrocortisone acetate on cardiac taurine content*.

		Taurine (μmoles/g wet wt)
Duration of treatment (n = 4)		
Control		21.3 ± 1.3
Hydrocortisone,	2 days	25,0 ± 0.6†
(20 mg/kg)	3	27.5 ± 2.0†
	4	28.6 ± 0.7†
	5	27.5 ± 1.0†
Dose-response (for 3 days, n = 6)		
Control		19.9 ± 0.6
Hydrocortisone,	2 mg/kg	24,0 ± 1.5
	10	26.1 ± 0.6‡
	20	25.5 ± 0.6‡

* Values are expressed as means ± S.E.
† $P < 0.05$, compared with the control value (Student's t-test).
‡ $P < 0.01$, compared with the control value (Student's t-test).

The taurine content in the heart also increases in dogs [16] and humans [13] with congestive heart failure, and in stress-induced hypertensive rats and spontaneously hypertensive rats [13]. However, the significance and the mechanism of these increases are not yet understood. Friedman *et al.* [17, 18] reported that chronic, but not acute, administration of glucocorticoids induced hypertension in rats. In this work we found that chronic injection of glucocorticoids induced a significant increase in the taurine content of the heart, but we failed to detect any effect of acute injection of hydrocortisone acetate on cardiac taurine content. These findings suggest a possible relation between hypertension and increase in cardiac taurine content in rats treated for long periods with glucocorticoids. To investigate this possibility, we determined the blood pressures of rats treated with hydrocortisone acetate. Systolic blood pressures of rats were raised gradually by repeated, but not by a single, administration of the drug (Table 3). This effect appears to parallel the increase in cardiac taurine content produced by the drug. Another effect of the steroid on cardiac taurine, independent of hypertensive effect, could not be excluded, though the present results might indicate a close relationship between cardiac taurine and blood pressure. These findings are of interest, in view of previous reports [19, 20] that taurine has a hypotensive action.

Table 3. Effect of hydrocortisone acetate on blood pressures of rats*

	Dose (mg/kg)	Blood pressure (mm Hg) Period of administration (days) 0	1	3	5	7
Sesame oil		91 ± 6	93 ± 6	90 ± 5	96 ± 5	99 ± 6
Hydrocortisone acetate	2	90 ± 4	92 ± 4	90 ± 5	110 ± 6†	106 ± 2‡
	10	88 ± 4	103 ± 4†	105 ± 6†	108 ± 7†	114 ± 5†
	20	92 ± 5	104 ± 8	114 ± 6†	125 ± 8‡	126 ± 4‡

* Each value is the mean ± S. E. of values in six animals.
† $P < 0.05$, compared with the value before the administration of hydrocortisone acetate (Student's t-test).
‡ $P < 0.01$, compared with the value before the administration of hydrocortisone acetate (Student's t-test).

Glucocorticoids also reduced weight gain. This may be due to their known catabolic action: they seem to induce an increase in free amino acids such as cysteine and methionine, precursors of taurine. So, it is possible that glucocorticoids increase the taurine content in the heart by increasing the levels of its precursors, although the metabolism of taurine in the heart is unknown. Another possibility is that transport of taurine into the heart is influenced by glucocorticoids.

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In vitro degradation of malathion by mouse liver*

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In a series of recent communications [1–3], it was reported that malathion [*0,0*-dimethyl *S*-(1,2-dicarbethoxyethyl) phosphorodithioate] was hydrolyzed by two types of esterases from mouse liver. Malathion B-esterase was predominantly in the microsomal fraction and had an optimum pH between 6.4 and 6.6. Malathion A-esterase was localized in the 100,000 *g* supernatant fraction, was insensitive to inhibition by organophosphates, required reduced glutathione (GSH) or similar SH compounds, and had an optimum pH of 8.8. The A-esterase was believed to degrade malathion at the P-S linkage resulting in the formation of *0,0*-dimethyl phosphorothioate even though no diethyl thiomalate was isolated. This raised the question of whether malathion A-esterase was truly a hydrolase or possibly another enzyme system and whether the colorimetric method [4] utilized in these studies could detect the metabolite formed in the 100,000 *g* supernatant fraction.

Experimental

Chemicals. [^{14}C]-malathion [*0,0*-dimethyl *S*-(1,2-dicarbethoxy [1,2-^{14}C] ethyl) phosphorodithioate] was purchased from Amersham/Searle (Arlington Heights, IL), with a specific activity of 32.2 mCi/m-mole. Non-radioactive paraoxon, malathion, malaoxon, malathion mono- and di-acids and desmethyl malathion [*0*-potassium, *0*-methyl *S*-(1,2-dicarbethoxyethyl) phosphorodithioate] were kindly donated by American Cyanamid Co., Agricultural Division, Princeton, NJ. Reduced glutathione was purchased from ICN Pharmaceutical (Cleveland, OH).

Enzyme preparation. Male mice, (20–25 *g*), N. C. Board of Health Strain, were decapitated and the livers removed and homogenized as 10% homogenates in 0.05 M Tris–HCl buffer, pH 8.8, at 0–4°. Differential centrifugation was carried out as described previously [5]. The 100,000 *g* supernatant fraction was dialyzed against 0.05 M Tris–HCl buffer, pH 8.8, for 20 hr at 4° to remove possible endogenous cofactors.

Reaction. The reaction mixture consisted of 1.0 ml of the 100,000 *g* supernatant fraction and 2 μmoles GSH in 0.05 M Tris–HCl buffer, pH 8.8. Two μmoles malathion was added, and the reaction mixture was incubated at 37° for 30 min. In some experiments, 0.2 μmole paraoxon was added and the reaction mixture preincubated at 37° for 15 min prior to the addition of malathion. The total volume of the reaction mixture was 2.0 ml. After incubation, the reaction mixture was partitioned against an equal volume of chloroform and the radioactivity determined in each phase. The aqueous phase was adjusted to pH 1 and then re-extracted with chloroform. The chloroform phase was dried over $MgSO_4$, then concentrated for thin-layer chromatography (t.l.c.).

Chromatography. The radioactivity in the chloroform extracts was separated initially by t.l.c. using 5 × 20 cm silica gel N-HR/UV-254 (0.25 mm precoated) plates utilizing benzene–ether–acetic acid (80 : 20 : 10, v/v) as solvent system I.

The metabolites were detected by scanning the t.l.c. plates on a Packard 7201 radiochromatogram scanner. Known

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