Acknowledgement—We gratefully acknowledge the valuable assistance of Michelle E. Mason and K. Charles Silinskas.

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Biochemical Pharmacology, Vol 27, pp 2972–2973

0006-2952/78/1215-2972 $02.00/0

Effects of prior administration of methionine sulfoximine on the thresholds of seizures induced in mice by 3-mercaptopropionic acid or pentylenetetrazol

(*Received* 9 *March* 1978; *accepted* 26 *April* 1978)

Attempts to disclose the mechanism by which methionine sulfoximine (MSO) induces convulsive seizures have revealed numerous effects on neurochemical processes but have not established a relationship between such effects and the occurrence of seizures [1–3]. Among the known effects are small or moderate decreases in the activity of glutamate decarboxylase (L-glutamate 1-carboxylyase, EC 4.1.1.15, GAD) [4–6] and the γ-aminobutyrate content of the brain [5–9]. That the GABA (γ-aminobutyric acid) system plays a role in the convulsive mechanism is strongly suggested by the report of Stransky [9], who found that the period of brain GABA depletion in MSO-treated rats coincided with that of sensitivity to audiogenic seizures. DaVanzo *et al.* [10] had noted previously that amino-oxyacetic acid strongly protects cats against MSO-induced seizures, presumably by increasing the brain GABA levels. Baumel *et al.* [11] observed that hypobaric hypoxia (which also raises the GABA level) protects mice from seizures induced by MSO, as well as from those induced by the GAD inhibitor, thiosemicarbazide.

We have obtained additional evidence that the effects of MSO on the GABA system may be responsible for the excitation, DL-Methionine-DL-sulfoximine (Sigma Chemical Co., St. Louis, MO) was dissolved in 0.9% NaCl and injected i.p. into mice in doses of 300 mg/kg. The latent period preceding seizures was found to be 3.5 hr or longer. In the latter part of the latent period, a subconvulsive excitatory state exists during which the 50 per cent convulsive dose (CD_{50}) values of convulsants with short latent periods can be determined.

Pentylenetetrazol (PTZ) or 3-mercaptopropionic acid (3-MP) was injected i.p. in graded doses 165 min after the administration of MSO, and the mice were observed for at least 30 min. The criteria used to indicate a convulsive response were a generalized clonic or tonic-clonic seizure with loss of righting reflexes. Latent periods were 2 to 9.5 min for seizures induced by PTZ, and 4 to 8 min for those induced by 3-MP. Log CD_{50} values were determined from probit-log dosage regression curves. The potency of each convulsant, when given after MSO, relative to that of the convulsant alone (ratio of potencies, essentially CD_{50} of convulsant alone/CD_{50} after MSO) was calculated and the 95 per cent confidence limits of log CD_{50} values and log potency ratios were determined. Further methodological details have been described previously [12].

The convulsive action of 3-MP is attributed to its inhibitory effect on GABA synthesis [13–16], while that of PTZ does not appear to involve the GABA system directly [17, 18]. It was noted previously that each of three GAD inhibitors (allylglycine, 4-deoxypyridoxine and thiocarbohydrazide), used in such a way as to induce a subconvulsive excitatory state, had a greater potentiating effect on the convulsive action of 3-MP than on that of PTZ [12]. The data in Table 1 show that MSO behaves in the same manner. This finding strengthens the hypothesis that the excitatory effects of MSO result from an action on the GABA system.

Although the mechanism of action of PTZ remains unclarified, studies on invertebrate preparations suggest that it generates prolonged depolarization shifts by directly altering membrane properties [19]. If this is true, the threshold to PTZ presumably would be altered nonspecifically by factors that influence the level of neuronal polarization, as seems to be the case [12].

Some convulsants are known to inhibit GAD activity by interfering with the synthesis or the coenzyme function of pyridoxal phosphate [13]. Seizures induced by such a mechanism can be inhibited or delayed by systemic administration of the coenzyme [20]. Accordingly, the following experiment was done.

Pyridoxal phosphate (Sigma) was freshly dissolved in water containing NaCl and Na_2CO_3 sufficient to make the final solution isotonic at pH 6. Six mice were given MSO (300 mg/kg) and, after 2 hr, pyridoxal phosphate in doses of 60 mg/kg, i.p. All had seizures; the mean latent period ± S.D.

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.

Acknowledgement—This work was supported in part by the Surgical Associates Fund, University of Wisconsin.

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Biochemical Pharmacology, Vol 27, pp. 2973–2975

0006-2952/78/1215-2973 $02.00/0

Increase of cardiac taurine by glucocorticoids

(*Received* 21 *September* 1977; *accepted* 3 *May* 1978)

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-