*Pharmacology Biochemistry & Behavior*, Vol. 21, pp. 491–493, 1984. © Ankho International Inc. Printed in the U.S.A. 0091-3057/84 $3.00 + .00

# The Effect of Repeated Electroconvulsive Shock on the Function of THIP, a GABA Agonist

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MINCHIN, M. C. W. AND D. J. NUTT. *The effect of repeated electroconvulsive shock on the function of THIP, a GABA agonist.* PHARMACOL BIOCHEM BEHAV **21**(4) 491–493, 1984.—Repeated electroconvulsive shock did not alter the anticonvulsant effect of THIP in rats, although it did elevate basal rectal temperature and abolish the hypothermic response to THIP.

Anticonvulsant Hypothermia THIP Electroconvulsive shock

REPEATED electroconvulsive shock (ECS) causes a number of behavioural effects in rats such as an increase in responses induced by 5-HT and dopamine [8] and a reduction in the effects of the $\alpha_2$-adrenoceptor agonist clonidine [11]. These effects are seen when ECS is given in ways similar to the administration of electroconvulsive therapy (ECT) [10] and thus may be of interest in establishing the mechanism of the antidepressant action of ECT. The effect of ECS on GABA function is less clear. *In vitro* binding studies suggest that high affinity GABA receptor number remains unchanged following ECS [1,7]. It has been shown that both single and repeated ECS cause a rise in regional brain GABA concentrations [3,4]. The seizure thresholds to pentylenetetrazol (PTZ) and a cage convulsant, both of which antagonise GABA indirectly, were unaltered after repeated ECS [5, 6, 15]. None of these findings excludes a change in GABA agonist function, particularly since some GABA functions may be mediated via a low affinity receptor, binding to which has been shown to alter following a variety of manipulations [2,17].

With the advent of GABA agonists capable of crossing the blood-brain barrier it has become possible to measure GABA receptor function *in vivo*, and we have investigated the effects of ECS on the anticonvulsant and hypothermic responses to THIP (4,5,6,7-tetrahydroisoxazolo[5,4-C]pyridin-3-ol) a GABA agonist [13] which crosses the blood-brain barrier and is moderately slowly metabolised [14].

## METHOD

Adult male Sprague-Dawley derived rats weighing 170–190 g were used throughout. ECS (125V, 1 sec, 50 Hz sinusoidal via earclip electrodes) was administered once daily for 10 days; sham-shocked animals had the earclips applied but no current was passed. Rectal temperature was measured with a thermocouple probe (Radiometer, Copenhagen), inserted to a depth of 4 cm.

Seizure threshold was measured using an intravenous infusion of PTZ [15], 30 min after injection of THIP. In ECS experiments measurements were made 24 hr after the last shock. The behavioural consequences of repeated ECS are apparent at this time although seizure threshold to PTZ is normal (see Introduction). The latter consideration is important because interpretation of the effect of THIP would be extremely difficult if the basal seizure threshold before and after ECS were different, as indeed they are at short times after ECS [16].

Pentylenetetrazol (Sigma) was used at a concentration of 10 mg/ml in saline. THIP was the generous gift of Lundbeck A/S, Copenhagen, and was dissolved in saline prior to IP injection.

## RESULTS

The dose-response curve for THIP against PTZ seizure threshold is shown in Fig. 1. A maximum anticonvulsant effect was not achieved at the highest dose of THIP used (20 mg/kg), which caused considerable sedation. All measurements were made 30 min after injection of THIP since we have shown that the maximal anticonvulsant effect occurs between 15 and 60 min post-injection.

Rats that had received 10 once-daily ECS showed the same elevated seizure threshold 30 min following a single dose of THIP as those that had been sham-shocked, when compared with controls that had received saline 30 min before seizure threshold measurement (Table 1). In sham-shocked controls THIP significantly depressed rectal temperature (Table 1), as it does in naive animals [9]. However, in the ECS-treated group a much smaller fall in temperature was observed, which was not significantly different from the

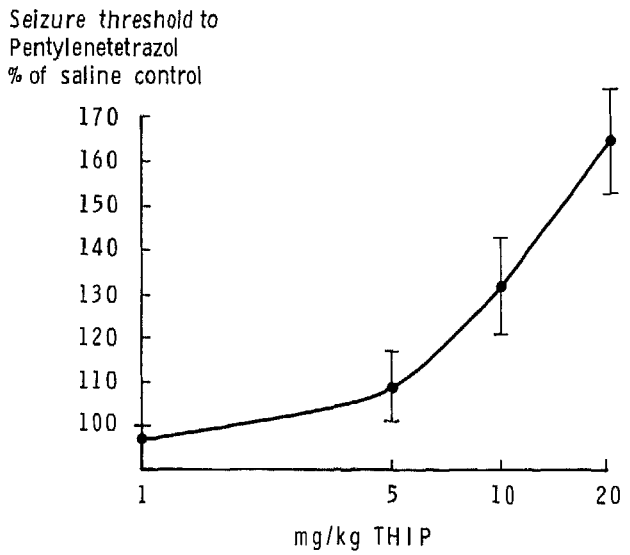


FIG. 1. Dose-response curve of the effect of THIP upon pentylenetetrazol-induced seizures. Rats were injected IP with various doses of THIP and 30 min later the seizure threshold to pentylenetetrazol was measured as described in Methods. Each point represents the mean±S.D. of 3 animals. Saline controls had a seizure threshold of 36±2 mg/kg pentylenetetrazol (mean±S.D. of 3 rats).

TABLE 1

EFFECT OF REPEATED ELECTROCONVULSIVE SHOCK ON RESPONSES TO THIP

(a) Seizure Threshold

| Treatment | Seizure Threshold (mg PTZ/kg) |
|---|---|
| Sham-Shocked, Saline | 30 ± 3 (5) |
| Sham-Shocked, THIP (10 mg/kg) | 42 ± 6 (6)* |
| ECS × 10, THIP (10 mg/kg) | 42 ± 3 (8)* |

(b) Hypothermia

| Treatment | Rectal Temperature, °C | |
|---|---|---|
| | Before THIP | 30 min after THIP (10 mg/kg) |
| Sham-Shocked ×10 | 37.4 ± 0.4 | 36.2 ± 0.9 (6)‡ |
| ECS × 10 | 38.1 ± 0.4† | 37.8 ± 0.5 (8) |

Rats were shocked or sham-shocked once daily for 10 days. Twenty-four hours after the last shock they were injected IP with either saline (1 ml/kg) or THIP (10 mg/kg) and temperature and seizure threshold to PTZ were measured 30 min later. Each value is the mean ± S.D. of the number of animals in parentheses. *$p<0.01$, 2-tailed $t$-test, compared with sham-shocked, saline injected controls.

†$p<0.01$ compared with sham-shocked controls, 2-tailed $t$-test.

‡$p<0.05$ compared with before THIP, 2-tailed paired $t$-test.

pre-THIP level. Interestingly, the ECS-treated group had a significantly higher basal temperature than the control group.

## DISCUSSION

The observation that repeated ECS did not alter sensitivity to the anticonvulsant effect of THIP suggests that the population of GABA receptors acted upon by THIP is not changed by this treatment. However, the finding that repeated ECS altered basal temperature and reduced the hypothermic effects of THIP may indicate a reduction of GABAergic tonic control in the thermoregulatory centre, possibly mediated by depressed sensitivity of GABA receptors in that region. An alternative possibility is that this change could reflect the well-known effect of ECS to increase 5-HT function. If this were to occur in the thermoregulatory centre (see [18]) resetting of a "thermostat" could result. THIP may act at other sites, for instance in those controlling heat loss and heat generation. These effects might be overridden by the influence of the thermostat, which could account for both the rise in basal temperature and the abolition of the hypothermic effect of THIP seen after ECS.

The observation that ECS raises basal temperature is a further indication that this treatment affects hypothalamic function. Other studies have shown that both eating and drinking behaviour [12] may be altered by repeated seizures. It would be of interest to see if changes in thermoregulation accompany the administration of electroconvulsive therapy, and if so, whether they correlate with therapeutic efficacy.

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