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Functional Responses to Baclofen and 4,5,6,7-Tetrahydroisoxazolo (5,4-c) Pyridin-3-ol (THIP) in Rats Repeatedly Treated With Desipramine

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BORSINI, F., S. GIULIANI AND A. MELI. *Functional responses to baclofen and 4,5,6,7-tetrahydroisoxazolo (5,4-c) pyridin-3-ol (THIP) in rats repeatedly treated with desipramine.* PHARMACOL BIOCHEM BEHAV **29**(1) 189–191, 1988.—Subcutaneous chronic desipramine (DMI, 5 mg/kg once daily for 18 consecutive days) prevented subcutaneous THIP (20 mg/kg) reduction in body temperature but did not affect THIP behavioral depressant effect (open-field behavior). Repeated DMI treatment did not affect subcutaneous baclofen (2.5–10 mg/kg) reduction in body temperature and behavioral depression (open-field behavior).

GABA Baclofen THIP Desipramine Functional responses Chronic treatment

RECENT evidence suggests that GABA may be involved in the mechanism of action of antidepressive treatments [1, 7, 9, 13]. Biochemical experiments have shown that repeated antidepressive treatments may cause up-regulation of GABA-B binding sites in the animal brain [7, 9, 13] without changing the number of GABA-A binding sites [9]. On the other hand, functional studies have shown that, unlike baclofen, THIP-induced antinociception was reduced in rats following repeated treatment with desipramine [3]. Moreover, the hypothermic effect of THIP but not its antagonism towards metrazole-induced convulsions was reduced in rats exposed to repeated electroshock [10]. Since THIP and baclofen are supposed to bind to GABA-A and GABA-B receptors respectively [8], it is possible that repeated antidepressive treatment may have caused, at least in some central nervous regions, a reduction in GABA-Aergic output. Therefore it appeared worthwhile to determine how repeated DMI administration would affect THIP and baclofen effect on open-field behavior and body temperature of rats.

METHOD

Animals

Male Wistar (Morini) rats, 250–300 g, were housed 4 to cage, at constant room temperature (21±1°C) and relative humidity (60%) with water and food ad lib, and a 12 hr light-dark cycle (light on: 6:00 a.m.). Each experimental group consisted of 7–8 rats and was chosen by means of a complete randomized schedule [2].

Functional Tests

The open field consisted of a conventional box [6]. One rat was placed in the corner of the box and the number of squares entered with all 4 paws and rearings within a 3 min period was recorded by an observer who was unaware of the treatment. Immediately after the end of open-field test, the rectal temperature was recorded by means of a thermocouple probe, inserted to a depth of 4 cm.

Experiments were carried out from 8:00 a.m. to 1 p.m.

Drug Treatment

Rats received subcutaneous saline (5 ml/kg) or DMI at a dose of 5 mg/kg acutely or once daily for 18 consecutive days. Saline (5 ml/kg), THIP (5 and 20 mg/kg) or (±)-baclofen (2.5 and 10 mg/kg) were administered subcutaneously 24 hr after a single or the last repeated dose of DMI. On the basis of preliminary experiments: (a) the open-field test was carried out 60 and 90 min after baclofen and THIP administration, respectively, and (b) the doses of the compound were selected to induce subthreshold and maximal effect.

Drugs and Sources

(±)-Baclofen and desipramine hydrochloride (Ciba-Geigy, Milan, Italy) and THIP (Lundbeck, Copenhagen, Denmark) were dissolved in saline.

Statistics

The data were analysed by factorial analysis of variance followed by Tukey test.

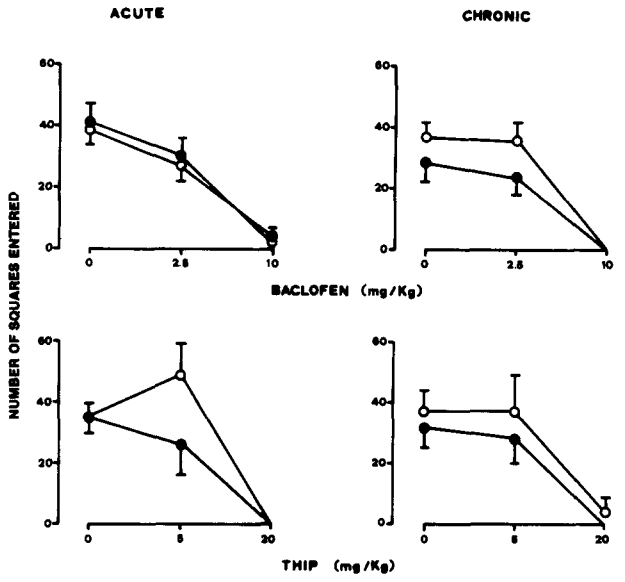

FIG. 1. Effect of acute and chronic treatment (18 days) with subcutaneous desipramine (5 mg/kg, once daily) on number of squares entered in an open-field by a rat after subcutaneous baclofen or THIP. Baclofen and THIP were administered 24 hr after the last injection of desipramine. The test was carried out 60 and 90 min after baclofen and THIP administration, respectively. Closed dots: desipramine-treated rats; open dots: vehicle-treated rats. Each point represents mean±s.e. from 7–8 rats.

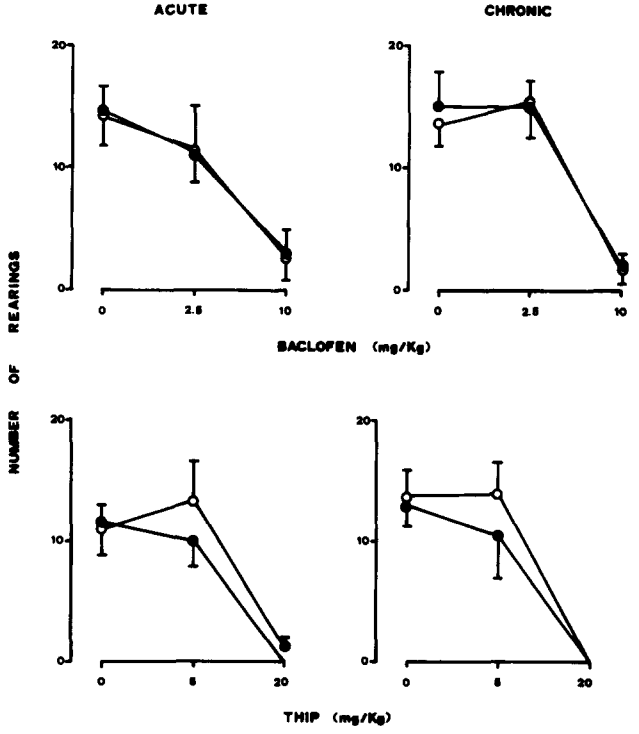

FIG. 2. Effect of acute and chronic treatment (18 days) with subcutaneous desipramine (5 mg/kg, once daily) on number of rearings by a rat in an open field after subcutaneous baclofen or THIP. Baclofen and THIP were administered 24 hr after the last injection of desipramine. The test was carried out 60 and 90 min after baclofen and THIP administration, respectively. Closed dots: desipramine-treated rats; open dots: vehicle-treated rats. Each point represents mean±s.e. from 7–8 rats.

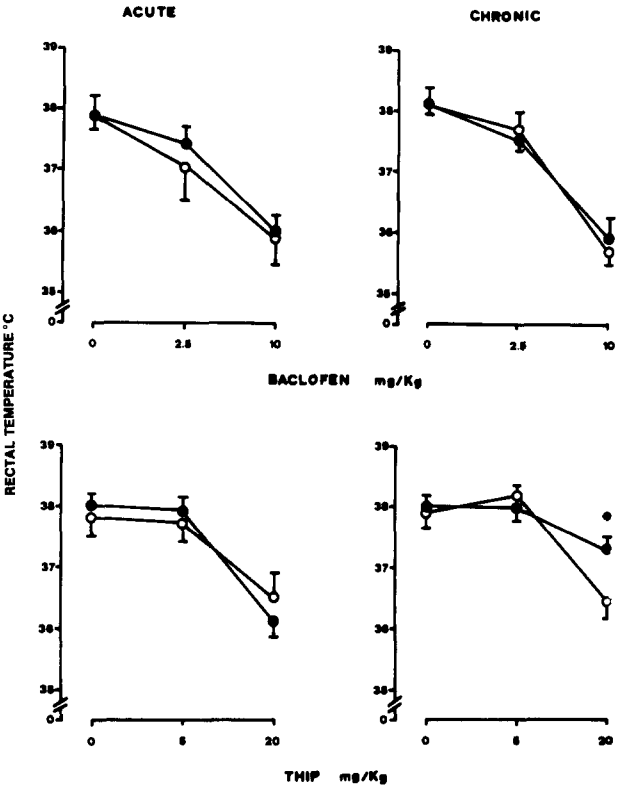

FIG. 3. Effect of acute and chronic treatment (18 days) with subcutaneous desipramine (5 mg/kg, once daily) on rectal temperature of a rat after subcutaneous baclofen or THIP. Baclofen and THIP were administered 24 hr after the last injection of desipramine. The test was carried out 60 and 90 min after baclofen and THIP administration, respectively. Closed dots: desipramine-treated rats; open dots: vehicle-treated rats. Each point represents mean±s.e. from 7–8 rats. *$p<0.05$ (ANOVA).

RESULTS

DMI (single or repeated dosing) did not affect the depressant effects of THIP and baclofen on open-field behavior (number of squares entered and rearings; Figs. 1 and 2). On the other hand, THIP (20 mg/kg) induced hypothermia was antagonized by repeated but not single administration of DMI, Fig. 3; ANOVA: $F(1,25)=4.31$, $p<0.05$. DMI treatment did not alter baclofen induced changes in behavior or body temperature (Figs. 1, 2 and 3).

DISCUSSION

Our findings indicate that DMI treatment was effective in antagonizing only THIP induced hypothermia. Our data obtained following repeated DMI administration agree well with the findings of Minchin and Nutt [10] who found that another type of antidepressive treatment (repeated electroshock) reduced the hypothermic effect of THIP. Since such a treatment did not induce any change in THIP anticonvulsant properties, it was suggested that this might have affected differently the sensitivity of GABA receptors upon which THIP acts.

Since THIP and baclofen appear to bind to GABA-A and GABA-B receptors respectively [8], we may hypothesize that chronic DMI influences, in different brain regions, sensitivity to GABA-A without affecting that of GABA-B recep-

tors, at least as regards the functions considered. Previous finding [3] indicated that chronic DMI reduced THIP but not baclofen antinociceptive effects. Therefore, it appears conceivable that the sensitivity of GABA-A, but not that of GABA-B receptors, is modified only in those CNS regions controlling temperature and nociception. Alternatively, DMI induced changes in the monoaminergic system [11] might account for the antagonism towards THIP hypothermic or antinociceptive effects. This hypothesis is supported by the observation that monoamines play a role in regulating temperature and nociception [4, 5, 12]. However, changes in monoaminergic function do not seem to interfere with baclofen effect on the above parameters nor do they play a role in THIP's effect on open-field behavior.

Although present results suggest that repeated DMI administration may reduce some functional responses due to activation of GABA-A but not GABA-B receptors, the mechanism responsible for this reduction remains to be clarified.

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