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Functional evidence for altered activity of gabaergic receptors following chronic desipramine treatment in rats

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The antinociceptive effect of subcutaneous 4,5,6,7-tetrahydroisoxazol[5,4-*c*]pyridin-3-ol (THIP) or (±)-baclofen, measured as reaction time of rats placed on a plate heated to 55 °C, was assessed after a single or the last repeated (18 consecutive days) dose (5 mg kg^{-1} once daily) of subcutaneous desipramine. Baclofen (10 mg kg^{-1})-induced antinociception was reduced by acute and unaffected by chronic desipramine treatment. On the contrary, THIP (20 mg kg^{-1})-induced antinociception was unaffected by acute and reduced by chronic desipramine.

Recent biochemical evidence suggests the involvement of GABA in the mechanism of action of antidepressants. A change in the number of brain GABA-A and GABA-B receptors has been observed in rats and mice following chronic treatment with antidepressant drugs (Pilc & Lloyd 1984; Lloyd et al 1985; Suzdak & Gianutsos 1985). We thought it worthwhile to check the responsiveness of GABA receptors in animals repeatedly administered with an antidepressant, by the use of a functional test. This was done in animals chronically treated with desipramine, by assessing the antinociceptive effect of 4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol (THIP) and (±)-baclofen, which are supposed to bind to GABA-A and GABA-B receptors, respectively (Hill & Bowery 1981).

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Method

Male Wistar Morini rats, 250–300 g, received subcutaneous THIP or baclofen 24 h after a single or the last repeated (18 consecutive days) dose (5 mg kg^{-1} once daily) of subcutaneous desipramine. The antinociceptive effect was assessed by recording the reaction time of a rat placed on a plate heated to 55 °C. On the basis of preliminary experiments: (a) the 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 antinociceptive effects.

Results and discussion

Baclofen-induced antinociception was reduced by acute and unaffected by chronic desipramine treatment (Fig. 1). Since reduction in noradrenergic function potentiates baclofen's antinociceptive effect (Sawynok 1984), the increased noradrenergic activity brought about by acute administration of desipramine might explain the reduced effect of baclofen. On the other hand, chronically administered desipramine induced desensitization of noradrenergic receptors (Racagni et al 1983) might be responsible for the restoration of baclofen antinociception.

Unlike baclofen, THIP-induced antinociception was unaffected by acute and reduced by chronic desipram-

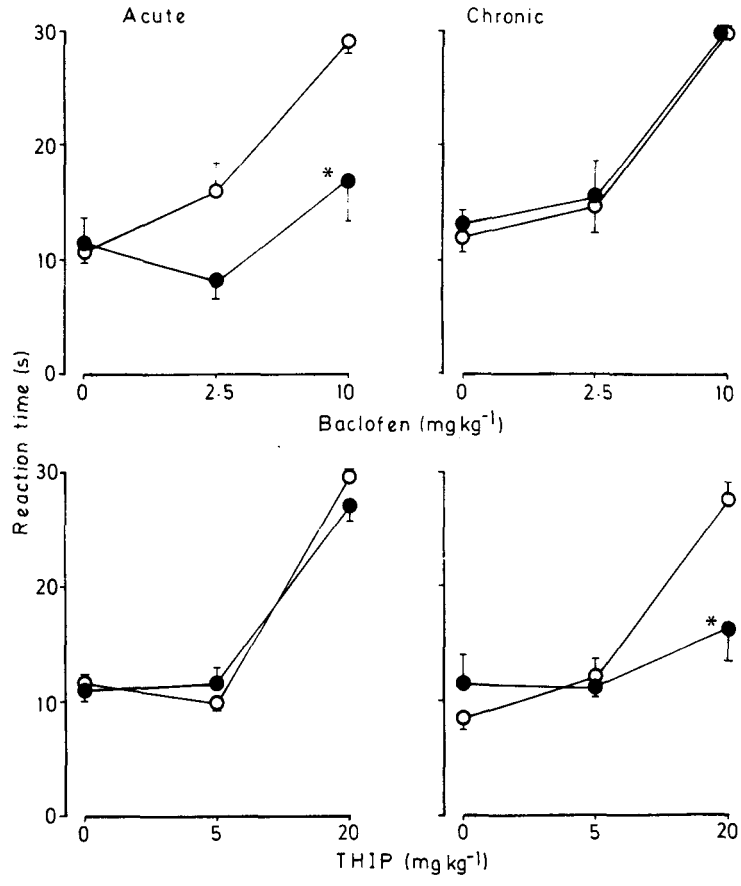

FIG. 1. Effect of acute and chronic treatment (18 days) with subcutaneous desipramine (5 mg kg^{-1}, once daily) on reaction time to nociceptive stimuli (plate heated to 55 °C) after subcutaneous baclofen or THIP. Baclofen and THIP were administered 24 h after the last injection of desipramine. The test was carried out 60 and 90 min after baclofen and THIP administration, respectively. Closed circles, desipramine-treated rats; open circles, saline-treated rats. Each point represents the mean ± s.e. of 8 rats. ANOVA (2 × 3) indicated a significant interaction between baclofen and acute desipramine ($P < 0{\cdot}05$; df = 2,42; F = 4·24) and between THIP and chronic despramine ($P < 0{\cdot}01$; df = 2,42; F = 7·2). Tukey test: * $P < 0{\cdot}01$ vs respective vehicle.

ine treatment (Fig. 1). Since acute desipramine did not alter the THIP effect, this suggests that increased noradrenergic activity does not play a major role in the development of THIP antinociception. On the other hand, the reduction in the THIP antinociceptive effect following chronic dosage of desipramine remains unexplained.

Since THIP and baclofen appear to bind to GABA-A and GABA-B receptors, respectively (Hill & Bowery 1981), the present results suggest that chronic, unlike acute, desipramine treatment reduces the activity of GABA-A receptors. On the other hand, the responsiveness of GABA-B is normalized by chronic treatment with desipramine.

Because baclofen and THIP seem to exert their antinociceptive effects at the spinal and supraspinal level, respectively (Hammond & Drower 1984), it is possible that different regional sensitivity to desipramine may be responsible for our findings.

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