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Triiodothyroacetic acid-induced reversal of learned helplessness in rats

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Triiodothyronine (T3), successfully used as therapeutic agent in euthyroid depressive states, has been found to exert an antidepressant-like effect in various psychopharmacological tests in rodents. Therefore the possible antidepressant-like activity of triiodothyroacetic acid (TA3), a natural metabolite of T3, was investigated in rats subjected to helplessness training. The animals were first exposed to inescapable shock pretreatment (60 shocks, 15 s duration, 0.8 mA every min ± 15 s) and 48 h later, shuttle-box training (30 trials/day, ITI: 30 s) was performed on 3 consecutive days in order to assess escape deficits. As compared to control rats (no shock pretreatment), the rats exposed to inescapable shocks exhibited escape deficits when tested for subsequent responding in the shuttle-box. Daily i.p. injections of TA3 (0.5 mg/kg) prevented escape deficits as did daily injections of tricyclic antidepressants. These data are in agreement with previous results bearing on the similarity of action of TA3 and tricyclic antidepressants and extend to the thyroid axis the neuroendocrine systems that can be affected by exposure to uncontrollable stressors.

Triiodothyroacetic acid; Learned helplessness; (Rat)

1. Introduction

The relationship between thyroid function and psychiatry is not limited to reciprocal interactions between mental disorders and thyroid status. Triiodothyronine (T3), successfully used as therapeutic agent in euthyroid depressive states (Prange et al., 1984 for a review), has been found to exert an antidepressant-like effect in various psychopharmacological tests in rodents (Brochet et al., submitted). Triiodothyroacetic acid (TA3) is a natural metabolite of T3 which is quite devoid of peripheral metabolic activity but exerts a strong inhibitory effect on TSH secretion (Greenberg et al., 1963).

An important question concerns whether TA3 has conserved the antidepressant-like activity of the hormone. This prompted us to investigate in rats the effect of TA3 in the learned helplessness test design, an animal model of depression that is highly sensitive to antidepressants and has been extensively used to study the neurobiological correlates of depressive states (Sherman and Petty, 1980; Hellhammer et al., 1984).

2. Materials and methods

The experiments were carried out on male Wistar A.F. rats (Centre d'élevage R. Janvier, France) weighing 175-200 g at the beginning of the experiments. The animals were housed in groups of 10/cage under standard conditions: room temperature (21 ± 1°C); light/dark cycle (12 h/12 h); water and food ad libitum.

2.1. Inescapable shock pretreatment

Electric footshocks were delivered in 20 × 10 × 10 cm chambers with plexiglas walls and cover. The floors were stainless steel grids (1.5 cm mesh). A constant current shocker was used to deliver 60

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scrambled, randomized inescapable shocks (15 s duration, 0.8 mA, every min ± 15 s) to the grid floor.

Control rats were placed for 1 h in identical chambers but no shocks were administered. Inescapable shock pretreatment was performed in the morning, on day 1.

2.2. Conditioned avoidance training

In order to evaluate the interference effect, avoidance training was initiated 48 h (day 3) after inescapable shock pretreatment in automated two-way shuttle-boxes (60 × 21 × 30 cm) with plexiglas walls and a floor consisting of stainless steel rods spaced 1.0 cm apart. Each shuttle-box was divided into two chambers of equal size by a stainless steel partition with a gate providing access to the adjacent compartment through a 7 × 7 cm space. The animals were placed singly in the shuttle-box, allowed to habituate to the test environment for 5 min (for the first session only) and were then subjected to 30 avoidance trials (inter-trial intervals of 30 s). During the first 3 s of each trial, a light signal (used as a conditioned stimulus (CS)) was presented, allowing the animals to avoid shocks. If a response did not occur within this 'CS only' period, a 3 s period with CS + electric footshock (0.8 mA) was presented. If no escape response occurred within this period, shock and light CS were terminated. The response (avoidance or escape) required of the rat was to cross the gate into the other compartment of the box. Although escape failure is defined as failure to escape within a 30-60 s period in most procedures used for helplessness assessement, the very first seconds following the start of shock seem to be critical for detecting interference effects in animal pre-exposed to inescapable shocks, especially under a simple FR1 schedule (Telner et al., 1981; Martin et al., 1986). Avoidance sessions were performed for 3 consecutive days (day 3, 4 and 5) in the morning and the number of escape failures, referred to as 'no crossing responses' during shock delivery, was recorded.

2.3. Drug administration

The rats were treated randomly according to one of the following protocols (10 rats per group): controls with no shock were given vehicle; experimental animals with inescapable shocks were injected daily with triiodoacetic acid (TA3) at 0, 0.115, 0.030, 0.060, 0.125, 0.250 or 0.500 mg/kg i.p. for 4 consecutive days (6 h after shock pretreatment or shuttle-box sessions). A possible effect of daily TA3 (0.5 mg/kg) on shuttle-box performance was also tested in a group of rats (n = 10) not pre-exposed to inescapable shocks. For comparison, additional groups of shocked rats (n = 10 per group) were given daily injections of desipramine and imipramine. The injections were performed 6 h after shock pretreatment then twice a day: in the morning (30 min before shuttle-box session) and the afternoon so that the daily dose for desipramine was 24 mg/kg (8 + 16) and 32 mg/kg (16 + 16) for imipramine. Doses and treatment schedules were chosen according to Massol et al. (1986) and Martin et al. (submitted).

3,5,3′-Triiodothyroacetic acid (TA3) (Ana, France) suspended in gum acacia (5%) and desipramine and imipramine (Ciba-Geigy) as a solution were injected in a volume of 0.5 ml/100 g body weight. Between group comparisons were made with a two-way analysis of variance (group and session) and Dunnett's one-tailed t-test.

3. Results

According to an analysis of variance of the data obtained on day 5 (fig. 1) non-treated rats pre-exposed to inescapable shocks showed more escape failures $F(1,230) = 20.13$, $P < 0.001$ than did the controls with no shocks. In rats pre-exposed to inescapable shock, daily administration of TA3 dose dependently reduced (linear regression $F(1,230) = 6.25$, $P < 0.02$) and, at 0.5 mg/kg, suppressed ($t = 5.57$, $P < 0.01$) escape failures. At this latter dose, TA3 significantly reduced escape failures in the first and second shuttle-box sessions ($t = 2.90$, $P < 0.05$; $t = 4.50$, $P < 0.01$, respectively). At 0.25 mg/kg TA3 just failed to reduce significantly escape deficits in the third shuttle-box session ($t = 2.63$) though a significant effect was observed (data not shown) in the second session ($t = 2.92$, $P < 0.05$).

These changes obtained with TA3 (0.5 mg/kg

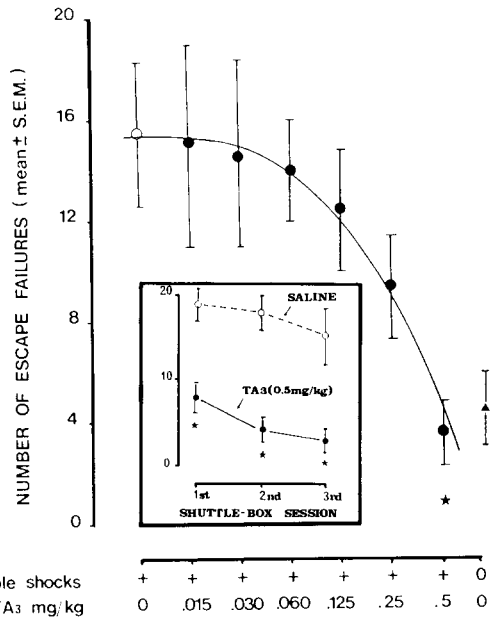

Fig. 1. Mean number of escape failures (± S.E.M.) during the 30 trials of the third daily shuttle-box session in control rats (▼) and in rats pre-exposed to inescapable shocks and injected daily with either saline (○) or TA3 (●), for 4 consecutive days (N = 10 rats/group). The doses indicated correspond to the total daily dose (mg/kg) injected i.p. on days 1, 2, 3 and 4. Escape failure refers to the failure of the rat to change compartment during the electric footshock (0.8 mA, 3 s duration). Inset: number of escape failures in TA3-treated rats (0.5 mg/kg per day) during the 3 consecutive daily shuttle-box sessions. * Indicates that after pre-exposure to inescapable shocks, the number of escape failures of treated rats differed from that of saline-treated animals at least at the 0.05 level (Dunnett's t-test).

per day) were similar to those observed in the third shuttle-box session with the tricyclic antidepressants imipramine (32 mg/kg per day) and desipramine (24 mg/kg per day) and inescapable shocks: + saline: 21.0 ± 2.5; + imipramine: 6.1 ± 2; + desipramine: 8.2 ± 1.5) (results not shown).

Finally, TA3 (0.5 mg/kg) did not alter shuttle-box performance in rats not subjected to learned helplessness training nor did this compound induce significant intertrial shuttling (data not shown).

4. Discussion

This study shows that rats pre-exposed to inescapable electric footshocks and treated with TA3 for 4 consecutive days did not exhibit an interference effect in the shuttle-box test. This protective, antidepressant-like effect was similar to that observed with conventional antidepressant drugs and with T3 (Martin et al., 1985) and seemed to affect deficit rather specifically since TA3 neither caused intertrial shuttling nor facilitated avoidance responding in rats not trained for learned helplessness. The doses required in this model were however slightly lower for T3 than for TA3, perhaps because of better brain penetration by the former compound. These findings suggest that the thyroid axis should be included among the neuroendocrine systems that can be affected by exposure to uncontrollable stressors (Hellhammer et al., 1984).

The neurobiological processes involved in the efficacy of TA3 on learned helplessness, an effect probably identical to that of T3, are still unknown. It can be suggested that through their ability to enhance the density of central α- and β-adrenoceptors (Gross et al., 1980), thyroid hormones may compensate for any deficient noradrenergic transmission that correlates with learned helplessness (Anisman et al., 1980; 1981). Such a compensatory effect could be amplified by an increased norepinephrine turnover such as that reported after an L-thyroxine regime (Engström et al., 1974).

This suggested noradrenergic mechanism of action of thyroid hormones would be consistent with the reported reversal by β-blocking drugs of the effects exerted by T3 in various psychopharmacological tests (Brochet et al., 1982; submitted).

These data obtained with experimental animals may have clinical implications. Since the first demonstration that the effect of imipramine treatment could be enhanced by thyroid hormone (Prange et al., 1969) various trials and case reports have confirmed the efficacy of T3 in the treatment of depression (see Prange et al., 1984 for a review). Thyroid hormones, however, are not commonly used in psychiatry because of their narrow therapeutic range, side-effects having been reported at

doses corresponding to the usual posology in psychiatric disorders (Earle, 1970; Goodwin et al., 1982; Gitlin, 1986).

Our results suggest that TA3 has conserved the central antidepressant-like properties of T3. Given the differences in the peripheral activity of TA3 and T3 (Greenberg et al., 1963) it can be assumed that the clinical use of TA3 would be easier than that of T3 in the treatment of depression.

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