BIOL PSYCHIATRY 1985;20:1023–1025

Triiodothyronine-Induced Reversal of Learned Helplessness in Rats

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Introduction

Affective disorders are the most commonly reported mental disturbances associated with frank hypothyroidism, and it has been reported that triiodothyronine (T3) given together with conventional antidepressants hastens recovery from depression or improves patients who had failed to respond to tricyclics (Charney et al. 1981; Goodwin et al. 1982; Schwarcz et al. 1984). This prompted us to investigate the effect of T3 on the learned helplessness paradigm in rats, 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, 1984; Hellhammer et al. 1984).

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 per cage under standard conditions: room temperature (21° ± 1°C), light/dark cycle (12 hr/12 hr), water and food ad libitum.

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Received March 18, 1985.

Inescapable Shock Pretreatment

Electric shocks to the feet were delivered in 25 × 20 × 10 cm chambers with plexiglass walls and cover. The floors were stainless steel grids (1.5-cm mesh). A constant-current shocker was used to deliver 60 scrambled, randomized inescapable shocks of 15 sec duration, 1 mA, every minute ± 15 sec to the grid flooring. Control rats were placed in identical chambers for 1 hr, but no shock was administered.

Conditioned Avoidance Training

Avoidance training was initiated 48 hr after inescapable shock pretreatment in automated two-way shuttle-boxes (60 × 21 × 30 cm) with plexiglass walls and a floor consisting of stainless-steel rods spaced 1.0 cm apart. Each shuttle-box was divided into two equal-sized chambers by a stainless steel partition, with a gate providing access to the adjacent compartment through a 7 × 7 cm opening. Animals were placed singly in the shuttle-box, allowed to habituate to the test environment for 5 min (for the first session only), and then subjected to 30 avoidance trials (intertrial intervals being 30 sec). During the first 3 sec of each trial, a light (used as a CS) was presented, allowing the animal to avoid shock. If a response did not occur within this period, a 1-mA shock (3 sec duration) was applied via the grid floor. If no escape response occurred within this latter period, shock and light CS were terminated. The response (avoidance or escape) required of the rat was to cross

0006-3223/85/$03.30

the gate into the other compartment of the box. Avoidance sessions were performed for 3 consecutive days in the morning, and the number of escape failures and of avoidances was recorded for each rat. Only data obtained during the last session are presented.

Drug Administration

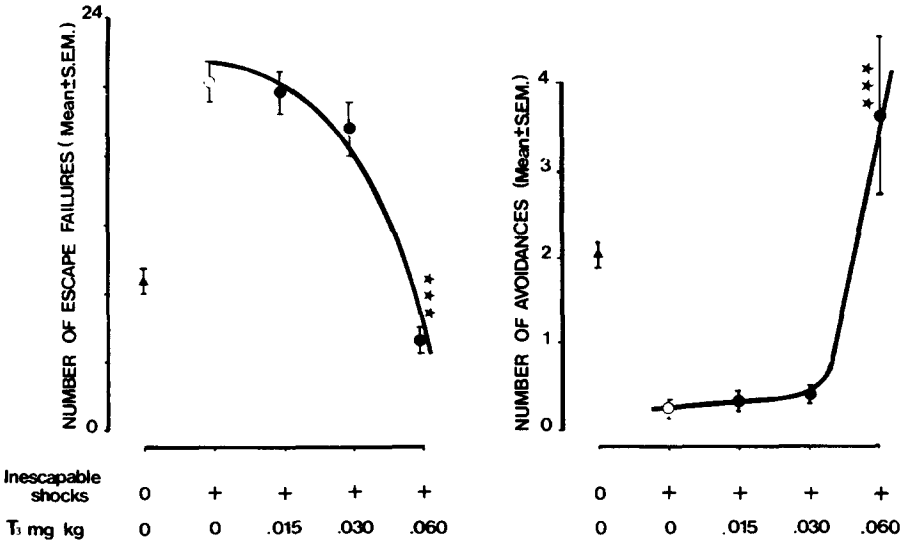
Rats were randomly treated according to one of the following protocols (16 rats per group): controls with no shock were given vehicle; experimental animals with inescapable shocks were injected daily with triiodothyronine (T3) at 0, 0.015, 0.030 or 0.060 mg/kg ip during 4 consecutive days (6 hr after shock pretreatment or shuttle-box session). Doses and treatment schedules were chosen as in our previous report (Brochet et al. 1982).

In order to assess possible actions of T3 on shuttle-box performance per se, one group of rats (n = 10) with no preexposure to shocks was injected daily at a dose of 0.06 mg/kg and tested for shuttle-box responses as previously described. T3 (Merrell Toraude/France) was suspended in acacia gum and injected intraperitoneally in a volume of 0.5 mg/100 g body weight. Between-group comparisons were made with analysis of variance and Dunnett's one-tailed t-test.

Results

Analysis of variance performed on data obtained at the third shuttle-box session (Fig. 1) revealed that nondrugged rats preexposed to inescapable shock exhibited more escape failures ($p < 0.01$) and fewer avoidance responses ($p < 0.001$) than controls with no shocks. In rats preexposed to inescapable shock, daily administration of T3 dose-dependently reduced (linear regression: $p < 0.02$) and, at 0.06 mg/kg, suppressed ($p < 0.01$) escape failures. Significant ($p < 0.01$) increases in the number of avoidance responses were also observed at the highest

Figure 1. Mean number (± SEM) of escape failures and avoidance responses during the third shuttle-box session (30 trials) in controls (inescapable shocks: 0) or in rats preexposed to inescapable shocks (+) and treated or not with triiodothyronine (T3). T3 was injected ip for 4 consecutive days. Escape failure refers to the absence of the response required of the rat to change compartments during the electric shock to the feet (1 mA, 3 sec); avoidance refers to the emission of such a response before shock delivery.***$p < 0.01$ as compared with rats preexposed to inescapable shocks and given vehicle.



dose studied. T3 (0.06 mg/kg) was not found to facilitate shuttle-box responses in rats not preexposed to inescapable shock (data not shown).

Discussion

This study shows that rats preexposed to inescapable electric foot-shocks and treated with triiodothyronine (T3) for 4 consecutive days did not exhibit escape and avoidance deficits when tested in the shuttle-box paradigm. This protective antidepressant-like effect seemed to affect deficit rather specifically, as T3 neither caused intertrial shuttling nor did it facilitate shuttle-box responses in animals not trained for learned helplessness. These findings extend to the thyroid axis the neuroendocrine systems that can be affected by exposure to uncontrollable stressors (Hellhammer et al. 1984).

In attempting to approach the neurobiological processes involved in the efficacy of T3 on learned helplessness, some hypotheses can be proposed. One possibility is that through its ability to enhance the density of central alpha- and beta-adrenoreceptors (see references in Charney et al. 1981 and Goodwin et al. 1982), T3 may compensate for any deficient noradrenergic transmission that correlates with learned helplessness (Anisman et al. 1980). Such a compensatory effect could be amplified by an increased noradrenaline turnover, such as that reported after a thyroxine (T4) regimen (Engstrom et al. 1974). Alternatively, escape failures have been found to be associated with a lowered activity of central serotonergic neurons, and, following tricyclic antidepressants, the reversal of helpless behavior correlated with an increased activity of these neurons (Sherman and Petty 1980, 1984). In agreement with investigations showing a positive relationship between thyroid function and serotonergic transmission (Engstrom et al. 1974; Vaccari et al. 1983), it is still conceivable that T3 treatment may reverse learned helplessness through its ability to restore serotonin transmission to an appropriate level.

In conclusion, our findings are consonant with clinical observations suggesting a deficient thyroid function in depressed patients. Numerous investigations have reported a blunted thyroid-stimulating hormone response to thyroid-releasing hormone, the normalization of which correlated positively with sustained clinical improvement (Charney et al. 1981). In addition, although T3 has not been reported to exhibit clear antidepressant activity in humans, it may accelerate or potentiate the effects of a variety of antidepressants (Charney et al. 1981; Goodwin et al. 1982; Schwarcz et al. 1984).

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