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Impaired Response of Experimental Diabetic Mice to Tricyclics: A Possible Beta-Adrenergic Mechanism

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MASSOL, J., P. MARTIN, F. CHATELAIN, P. SOUBRIÉ AND A.-J. PUECH. *Impaired response of experimental diabetic mice to tricyclics: A possible beta-adrenergic mechanism.* PHARMACOL BIOCHEM BEHAV **31**(4) 807–812, 1988.—Diabetes is reportedly associated with alterations in peripheral and central noradrenergic systems. The latter might be involved in the antidepressant effects of imipramine-like drugs in both humans and animals. Therefore, it is possible that diabetics show an impaired responsiveness to tricyclics. To test this possibility the effects of streptozotocin (STZ)-induced experimental diabetes in mice were assessed in two psychopharmacological tests: 1) the reversal of apomorphine- (16 mg/kg) induced hypothermia and 2) the hypoactivity induced by a direct beta-agonist (clenbuterol 0.06 mg/kg). At day 15 after STZ or vehicle treatment, imipramine (4 mg/kg) antagonized the apomorphine-induced hypothermia in diabetic (D) and nondiabetic (ND) mice and clenbuterol produced hypoactivity in both groups. At day 30 and 45, the ability of imipramine (1, 2, 4, 8, 16 mg/kg), clomipramine (8 mg/kg) and desipramine (2 mg/kg) to reverse apomorphine-induced hypothermia disappeared at the same time that clenbuterol lost its ability to induce hypomotility in D mice. These impaired responses on both tests were corrected by a short period of insulin therapy. These two tests may reflect central beta-adrenergic functions. Therefore, these data suggest that the impaired responsiveness of diabetic mice might be due at least in part to a noradrenergic dysfunction. Possibly, in diabetes, a beta-adrenoceptor desensitization identical to that observed at the peripheral level occurs in the central nervous system. The possibility that a thyroid hormone deficiency may be involved was also tested. Decreased T3 plasma levels were found in D mice concomitant with the impaired pharmacological responses and T3 supplementation turned these responses to normal. An hypothetical link between these thyroid effects and the beta-adrenergic desensitization in D mice could be suggested but remains to be determined.

Experimental diabetes Tricyclics Beta-adrenoreceptors Thyroid hormone

DIABETICS are at risk for depressive illness (30). For this reason, they are probably given antidepressant drug treatments more often than the general population.

Evidence suggests that normal central monoaminergic and particularly noradrenergic functions are required for antidepressive activity of tricyclics (9). Other evidence indicates that noradrenergic function may be impaired in diabetes (3, 4, 48–50).

Therefore, it is possible that diabetics show an impaired responsiveness to tricyclics. The present experiment was undertaken to test this hypothesis by examining the responsiveness of diabetic mice to tricyclics in a paradigm previously shown to be responsive to antidepressent drugs (ADS), viz., apomorphine-induced hypothermia (38).

Results revealed that diabetic mice were significantly less responsive to tricyclics than controls. A second series of experiments was carried out to test the possibility that this decreased responsiveness was related to a beta-adrenergic dysfunction. Previous studies have shown that the beta-adrenergic agonist clenbuterol decreases locomotor activity in nondiabetic mice (14). Thus, the effects of clenbuterol on the locomotor activity of diabetic and control mice were tested.

This beta-receptor alteration could be linked to a thyroid hormone deficiency (19). Indeed, a low triiodothyronine (T3) syndrome has been described in diabetic patients (18,35) as well as in experimental diabetes (45). The third study was carried out to test the possibility that, under T3 treatment, diabetic mice became responsive to tricyclics or clenbuterol.

METHOD

Animals

Male Swiss NMRI mice (20–24 g before experiments),

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from CERJ-Genest, St. Isle 53940 France, were used in all experiments. Mice were housed in groups of 10, divided into homogeneous subgroups of controls, nondiabetics (ND) and diabetics (D), with a 12-hour light-dark schedule (light on at 8.00 hr) in a room thermostatically maintained at 21±1°C. Food and water were freely available.

Diabetes was experimentally induced by injecting streptozotocin (Upjohn) as previously reported (39). Briefly, streptozotocin (STZ) was dissolved in 0.05 M citrate buffer (pH 4.5) and immediately injected (IP) at a dose of 200 mg/kg in a volume of 0.25 ml/20 g body weight.

The presence of diabetes was confirmed 48 hours later by semiquantitative detection of glycosuria (Ames Strips).

A subgroup of diabetic mice (ID) was treated every evening (at 18.00 hr) for a week before testing with slow insulin (NOVO) (0.1 UI/g/day; SC). The last insulin injection was performed 12 hours before the test.

Drugs

Clomipramine, desipramine, imipramine (Ciba Geigy) and clenbuterol chloride (Boehringer Ingelheim) were dissolved in distilled water.

Triiodothyronine (T3) (Merrell Toraude) was suspended in aqueous acacia gum (5%) and administered IP. T3-treated mice received one injection per day for three days, according to Brochet *et al.* (7). There was a 24-hour delay between the last administration and each test.

Controls were injected with distilled water. All injections (IP) were performed in a volume of 0.25 ml/20 g body weight.

Method

The reversal by tricyclics of apomorphine-induced hypothermia was performed according to Puech et al. *(38).* The animals (D and ND) were given either tricyclics or saline 30 minutes before apomorphine (Coopération Pharmaceutique Française) (16 mg/kg; SC) and then isolated in small transparent boxes (10×6×4 cm). Rectal temperature was measured 30 minutes after apomorphine administration.

In the first experiment, imipramine (4 mg/kg; IP) was used at different stages of diabetes (Day 15, D30, D45).

In a second experiment a dose range of imipramine (1, 2, 4, 8, 16 mg/kg), clomipramine (8 mg/kg) and desipramine (2 mg/kg) were tested at D30.

In a third experiment desipramine (2 mg/kg) was tested after a T3 pretreatment (0.125 mg/kg) at D30.

Reduction of locomotor activity caused by clenbuterol. The motor activity of each mouse was recorded individually in a photocell actimeter (6) and results were expressed as the number of beams crossed during 30 minutes. ND and D animals were treated with clenbuterol (0.06 mg/kg) 30 minutes before testing. The first experiment was performed at D15, 30 and 45. The same experiment was repeated on D30 after a pretreatment of T3 (0.06 or 0.125 mg/kg/day).

Thyroid hormone assays. Free serum T3 and thyrotropic stimulating hormone (TSH) were measured by simultaneous double antibody radioimmunoassay (R.I.A.) methods based on those of Ellis and Ekins (11) using commercial kits (CEA France). All determinations employed batch analysis of the serum samples for each animal and were run in duplicate. These samples were collected at the end of the tests.

Statistics

Statistical analysis was performed using the Student's *t*-test.

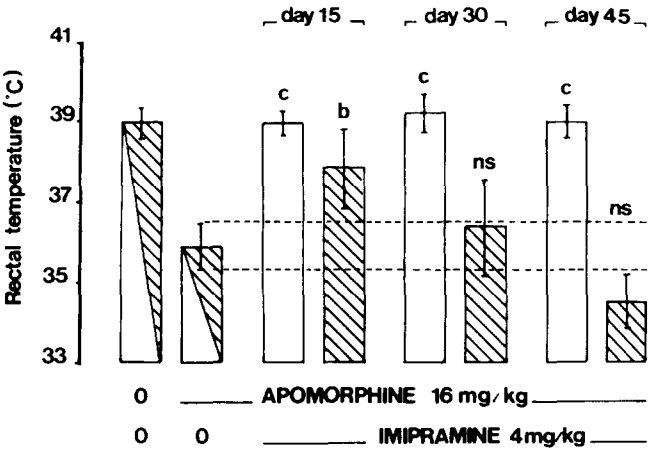

FIG. 1. Reversal of imipramine (4 mg/kg; IP) of apomorphine- (16 mg/kg; SC) induced hypothermia in nondiabetic (open bars) and diabetic (hatched bars) mice at the 15th, 30th and 45th days after injection of streptozotocin (200 mg/kg; IP) or saline. Values represent rectal temperature (mean±SEM) recorded 30 minutes after apomorphine treatment (8 mice/group). Letters indicate that in mice given apomorphine, nondiabetics and diabetics, imipramine-treated animals differ significantly from saline-treated (half-open/half-hatched bar). $^{b}p<0.01$, $^{c}p<0.001$; ns: nonsignificant.

RESULTS

For clarity, D and ND control values of both tests were pooled.

Reversal by tricyclics of apomorphine-induced hypothermia. In the first experiment (Fig. 1), on day 15, imipramine (4 mg/kg) significantly antagonised the hypothermia induced by apomorphine in groups ND ($p<0.001$) and D ($p<0.01$), while on days 30 and 45, the expected antagonistic effect of imipramine was observed in group ND ($p<0.001$) but not in group D (ns).

In the second experiment (Fig. 2), performed on day 30, imipramine (1, 2, 4, 8, 16 mg/kg) exerted a dose-dependent antagonism in both groups. However, in ND mice, this effect was significant from the dose of 1 mg/kg, whereas in D mice this antagonism was significant only from the dose of 8 mg/kg ($p<0.05$) and reached the full effect at 16 mg/kg (vs. 2 mg in ND mice). On day 30, clomipramine (8 mg/kg) and desipramine (2 mg/kg) where found to be as effective as imipramine for antagonizing apomorphine-induced hypothermia in ND mice. However, neither was able to reverse the hypothermia in D mice (Fig. 2).

In the third experiment, on day 30, pretreatment with T3 (0.125 mg/kg) restored the antagonistic effect of desipramine (2 mg/kg) in D mice (Fig. 3).

Reduction of locomotor activity caused by clenbuterol. On day 15, clenbuterol significantly decreased ($p<0.001$) locomotor activity in group ND and D mice (Fig. 4). However, on days 30 and 45, whereas clenbuterol was still able to decrease motor activity in group ND ($p<0.001$), this was not the case in D mice (Fig. 4).

On day 30, a pretreatment by T3 (either 0.06 or 0.125 mg/kg/day) (doses which were ineffective in ND mice when T3 is given alone) restored the hypomotility induced by clenbuterol (0.06 mg/kg) (Fig. 5).

Thyroid hormone assays. Thyroid hormone assays performed at day 30 revealed a significant decrease ($p<0.001$) in T3 plasma levels in D mice (2.66±0.35 vs. 4.24±0.32

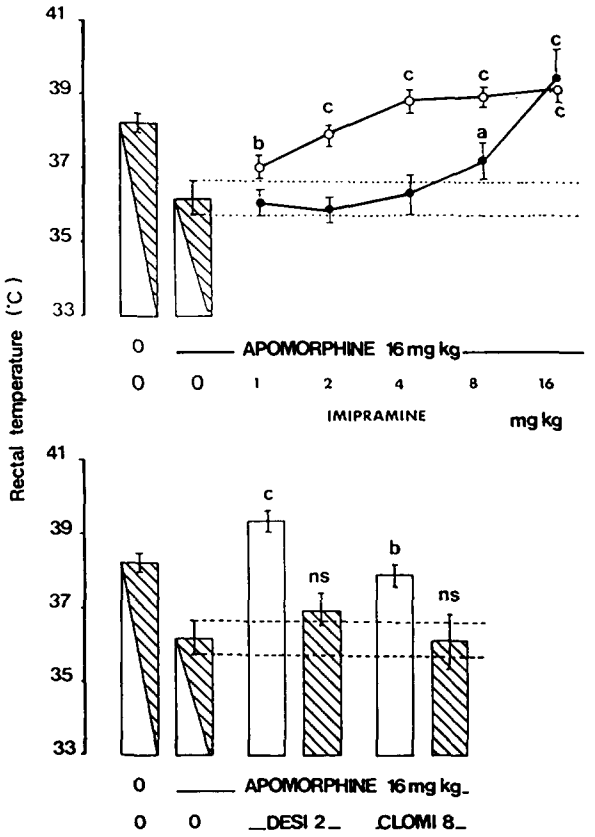

FIG. 2. Reversal of apomorphine- (16 mg/kg; SC) induced hypothermia in nondiabetic (open circle or open bar) and diabetic (closed circle or hatched bar) mice at the 30th day after injection of streptozotocin (200 mg/kg; IP) or saline by: 1) a dose range of imipramine (1, 2, 4, 8, 16 mg/kg; IP); 2) desipramine (2 mg/kg; IP); 3) clomipramine (8 mg/kg; IP). Values represent rectal temperature (mean±SEM) recorded 30 minutes after apomorphine treatment (8 mice/group). Letters indicate that in mice given apomorphine, nondiabetics and diabetics, tricyclics-treated animals differ significantly from saline-treated (half-open/half-hatched bar). $^{a}p<0.05$, $^{b}p<0.01$, $^{c}p<0.001$; ns: nonsignificant.

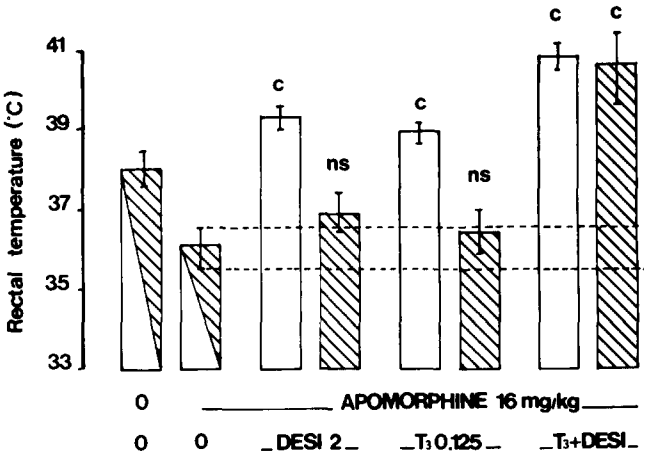

FIG. 3. Effects of desipramine (2 mg/kg; IP) and triiodothyronine (T3) alone (0.125 mg/kg/day) (see the Method section) on apomorphine-induced hypothermia in nondiabetic (open bars) and diabetic (hatched bars) mice at the 30th day after injection of streptozotocin (200 mg/kg; IP) or saline. Influence of a T3 treatment (3 days) in interaction with desipramine (2 mg/kg; IP). Values represent rectal temperature (mean±SEM) recorded 30 minutes after apomorphine treatment (8 mice/group). Letters indicate that in mice given apomorphine, desipramine alone, T3 alone, desipramine + T3, nondiabetics and diabetics, treated animals differ significantly from saline-treated (half-open/half-hatched bars). $^{c}p<0.001$; ns: nonsignificant.

pmoles/l in ND mice). TSH plasma levels were not significantly different (1.74±0.11 vs. 1.71±0.23) in D and ND mice.

The effects of insulin therapy. A short period of insulin therapy (a week) prevented the diabetic mice from exhibiting the resistance to both reversal of apomorphine-induced hypothermia by imipramine and the clenbuterol-induced hypomotility (Table 1).

DISCUSSION

The antagonism of apomorphine- (16 mg/kg) induced hypothermia is a standard test for screening potential antidepressants (25, 36–38).

In the present study, the magnitude of the hypothermia induced by apomorphine was of the same order in D and ND mice, the antagonistic effect of imipramine was preserved at the 15th day of diabetes duration showing that both groups were initially responsive to this treatment. However, at the 30th and 45th day, imipramine reversal of apomorphine-induced hypothermia could only be achieved in D mice with

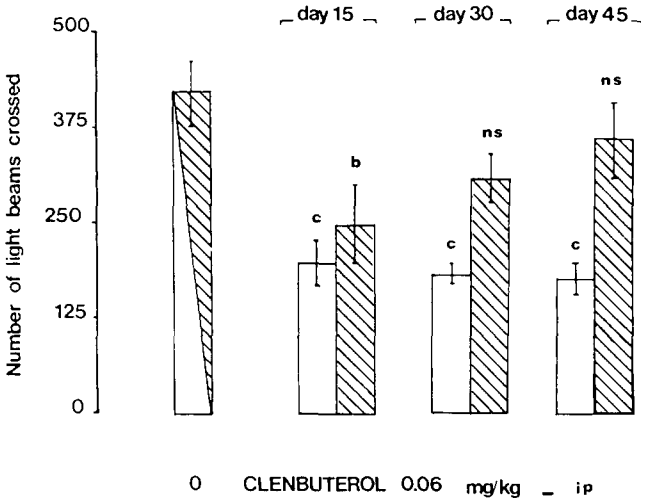

FIG. 4. Effects of clenbuterol on locomotor activity in nondiabetic (open bars) and diabetic (hatched bars) mice, at the 15th, 30th and 45th days after injection of streptozotocin (200 mg/kg; IP). Values represent the mean number (±SEM) of light beams crossed over a 30-minute period, 30 minutes following clenbuterol administration (0.06 mg/kg; IP). Letters indicate that mice given clenbuterol differ significantly from saline-treated controls (half-open/half-hatched bars). $^{b}p<0.01$, $^{c}p<0.001$; ns: nonsignificant.

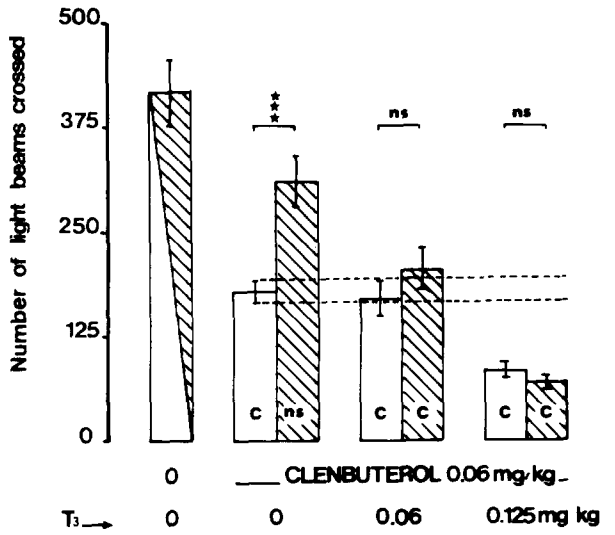

FIG. 5. Effects of clenbuterol alone on locomotor activity in non-diabetic (open bars) and diabetic (hatched bars) mice, at the 30th day after injection of streptozotocin (200 mg/kg; IP) or saline. The influence of a T3 pretreatment (0.06 or 0.125 mg/kg during 3 days; see the Method section) in interaction with clenbuterol (0.06 mg/kg; IP). Values represent the mean number (±SEM) of light beams crossed over a 30-minute period, 30 minutes following clenbuterol administration (0.06 mg/kg; IP). Letters indicate that mice given clenbuterol differ significantly from saline-treated controls (half-open/half-hatched bars). $^{c}p<0.001$; ns: nonsignificant.

an eight times higher dose regimen than that able to give a full effect in ND mice (16 vs. 2 mg/kg). The observed resistance of D mice to the action of tricyclics is in good agreement with our previous finding that tricyclics failed to reverse learned helplessness in D rats at the same stage of evolution of the STZ-induced diabetes (28,29). These results raise the question of a similar resistance in human diabetes.

The mechanism of this resistance in D mice is unknown. In D rats, no differences in the pharmacokinetics of ADS could explain this resistance (in press). Since the high dose of apomorphine-induced hypothermia and its antagonism in ND mice seems to be related to an interaction with a beta-adrenergic rather than to a dopaminergic system (37), it was hypothesized that a beta-adrenergic dysfunction could also contribute to the explanation of the observed resistance in D mice. In agreement with this view, it was found that diabetic mice exhibited a concomitant resistance to the hypomotility induced by clenbuterol which has been demonstrated to be mediated by a central beta-adrenergic mechanism (14). It therefore seemed likely that a central beta-adrenergic desentization could participate in the resistance of D animals to ADS. Such a desensitization would agree with that observed at the peripheral levels particularly in the heart [see (17,24)] and other tissues (21,23) of diabetic rats, or more recently in mononuclear leucocytes of juvenile insulin dependent diabetic patients (33). The mechanisms involving such a possible peripheral as well as central (according to the present study) noradrenergic deficiency are unknown.

Since many evidences exist indicating that the central noradrenergic systems are hypoactive in experimental diabetes (4,51), this desensitization is unlikely to result from a down-regulation mechanism. Glucose by itself has been shown to depress noradrenergic transmission (12,26). However, present findings cannot be attributed to acute hyperglycemia since the effects were not present on day 15 when hyperglycemia had already been stabilized. Insofar as

TABLE 1

EFFECTS OF INSULIN (0.01 UI/g/DAY: SC) THERAPY (SEE THE METHOD SECTION) ON THE REVERSAL BY IMIPRAMINE (4 mg/kg; IP) OF APOMORPHINE- (16 mg/kg; SC) INDUCED HYPOTHERMIA AND ON THE EFFECTS OF CLENBUTEROL (0.06 mg/kg; IP) ON LOCOMOTOR ACTIVITY IN NONDIABETIC (ND), DIABETIC (D) AND DIABETIC + INSULIN (DI) MICE, AT THE 30th DAY AFTER INJECTION OF STREPTOZOTOCIN (200 mg/kg; IP) OR SALINE

	Effects of Insulin Therapy (0.1 UI/g/day)	
	Reversal by Imipramine of Apomorphine-Induced Hypothermia: Rectal Temperature °C (mean ± SEM)	Clenbuterol-Induced Hypomotility: Number of Light Beams Crossed (mean ± SEM)
Controls (ND + D + DI)	35.7 ± 0.5	420 ± 41
Nondiabetics (ND)	39.2 ± 0.4*	179 ± 13*
Diabetics (D)	35.0 ± 0.9 ns	309 ± 33 ns
Diabetics + Insulin (DI)	39.9 ± 0.5*	174 ± 25*

*$p<0.001$; ns: nonsignificant.

Values represent rectal temperature (mean ± SEM) and the mean number (±SEM) of light beams crossed. Asterisks indicate that mice ND and DI differ significantly from controls (ND + D + DI).

insulin has been shown to enhance central noradrenergic turnover (1), insulin deficiency probably plays a causal role in the decreased noradrenergic transmission of diabetic states. Concomitant impaired beta-adrenergic responsiveness and decreased availability of noradrenaline in diabetes would agree with a defective beta-adrenergic up-regulation hypothesis. However, this remains to be demonstrated. A thyroid hormone deficiency such as that reported in diabetes (40,42) and verified in the present study might account for the suggested beta-adrenergic desensitization. Indeed, hypothyroidism has been found to be associated with a reduced responsiveness of peripheral and central noradrenergic systems (19). Moreover, a T3 regimen has been reported to enhance the response to noradrenergic agents and the density of beta-adrenergic receptors (2, 15, 34). In the present study, a temporal relationship was found between the altered response to tricyclics and clenbuterol and a decreased plasma level of T3. Furthermore, it was found that a T3 supplementation restored the responsiveness of diabetic mice in both tests.

The fact that insulin treatment prevented our diabetic mice from exhibiting the apparent noradrenergic deficiency lends further support to the suggestion that T3 plays a crucial role in noradrenergic anomalies associated with diabetes. Indeed, Sundaresan *et al.* (45) have found that insulin administration restored normal T3 levels in diabetic rats and concomitantly eliminated the alterations in myocardial beta-adrenergic function, except in thyroidectomized rats.

However, the consistency of the hypothesis that diabetes-induced beta-adrenergic desensitization is due to thyroid hormone deficiency has to be discussed. Indeed, most of the authors have shown similar beta-adrenergic desensitization in hypothyroidism [see (2) for a review] and diabetes (41). However, the appreciation of the alpha-adrenergic function has been controversial. Some authors have reported discrepant alpha-adrenergic density [increased in hypothyroidism (8) and decreased in diabetes (20)], while others have reported similar decreased density (32) and increased responsiveness in both hypothyroidism and diabetes (10,22). Thus, the question remains answered.

Nevertheless, though it cannot be ascertained that the thyroid disturbances seen in diabetes play a causal role in the impaired responsiveness of diabetic animals to the antidepressants, it can be assumed that T3 therapy may restore this responsiveness just as it has been shown that it can restore or prevent (13) some cardiac abnormalities of experimental diabetes (47).

When considering the presented impaired response of diabetic animals to the antidepressants, a crucial point to be taken into account is the weight loss. As a matter of fact, it has previously been shown that even a slight weight loss, just as that occurring in experimental diabetes, could be a critical intervening factor in the delayed response to antidepressants (43). The fact that decreased T3 plasma levels (low T3 syndrome) and altered noradrenergic transmission [reduced noradrenaline turnover (51)] reduced beta-adrenergic receptor density (31) were found to be linked to starvation and the additional facts that T3 therapy was found able 1) to reverse the impaired response of starved rats to antidepressants (43) and 2) to partly offset the decrease in the number of beta-adrenergic receptors (31) supported the T3-mediated beta-adrenergic hypothesis and should permit to extend the discussion of the present impaired response to antidepressants to other low-T3 syndrome linked pathological states other than diabetes (27).

In conclusion, this study reports an abnormal pharmacological response of diabetic mice that might be related to a beta-receptor-mediated anomaly of central noradrenergic transmission. Together with previous studies, our results support the notion of extensive alterations of peripheral, or central noradrenergic system, in D mice. From a practical point of view, these data might suggest that diabetic subjects, who are at high risk for depressive states (30, 44, 46), could be resistant to tricyclics at least in poor metabolic control states. To our knowledge, no such resistance has been reported. Nevertheless, if this was demonstrated to be the case, in light of the present data and the fact that T3 reportedly converts tricyclic nonresponders to responders (16), this hormone could be an appropriate adjunctive treatment in diabetic patients.

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