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Effects of Acute and Long-Term Treatments With Thyrotropin-Releasing Hormone on Locomotor Activity and Jumping Behavior in Mice

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USHIJIMA, I., Y. MIZUKI, T. HARA, K. WATANABE, H. HIRANO, M. YAMADA AND G. B. GLAVIN. *Effects of acute and long-term treatments with thyrotropin-releasing hormone on locomotor activity and jumping behavior in mice.* PHARMACOL BIOCHEM BEHAV **24**(5) 1423–1428, 1986.—The acute and chronic effects of thyrotropin-releasing hormone (TRH) on ambulation and, in combination with apomorphine, on jumping behavior were investigated in mice. A single administration of TRH (1–10 mg/kg SC) produced an initial hyperactivity in a dose-dependent manner. Following administration of TRH (1–10 mg/kg SC) for 21 successive days, the stimulatory effect on locomotion progressively increased. Haloperidol exerted a biphasic action on hyperlocomotion induced by acute and repeated TRH, i.e., stimulation at lower doses (0.01–0.02 mg/kg SC) and inhibition at higher doses (0.05–1 mg/kg SC). When TRH was administered in combination with low doses of apomorphine, locomotor activity was inhibited but jumping behavior occurred. The inhibitory effect of low doses of apomorphine on locomotion was shifted from doses of 0.1–0.25 mg/kg SC of apomorphine for acute TRH (10 mg/kg) to 0.25–0.35 mg/kg for repeated TRH (10 mg/kg), whereas the stimulatory effect of higher doses of apomorphine (0.5–1 mg/kg SC) on locomotion tended to decrease with repeated TRH. Jumping behavior induced by the combined treatment of TRH and apomorphine was proportional to the dose of TRH but exhibited an inverted-U response to the dose of apomorphine. Chronic TRH (10 mg/kg) in combination with apomorphine (0.1–1 mg/kg SC) also produced jumping behavior, but the dose-response curve for apomorphine was shifted to the right. The present results suggest that repeated treatment with TRH in mice produces hyperlocomotion, despite attenuation of both pre- and postsynaptic receptor activity, and that the inhibitory effect of repeated TRH on presynaptic receptors may be more potent than that on postsynaptic receptors.

Thyrotropin-releasing hormone Dopamine Dopamine receptor Presynaptic receptors
Acute vs. chronic effects Locomotor activity Jumping behavior Mouse

THYROTROPIN-RELEASING hormone (TRH) stimulates the release of thyrotropin [2] and prolactin [5]. TRH is also thought to play an important role as a neuropeptide in the central nervous system, as suggested by a number of behavioral and biochemical studies [13,23].

TRH injected into the nucleus accumbens of rats produces dopamine-like locomotor activity and behavioral changes [9,20]. Intraperitoneal injection of TRH induces effects similar to those observed after central injection of TRH in rats [10,20] and in mice [32, 33, 35], i.e., initial hyperlocomotion, tremors, salivation, Straub tail, and stereotypy such as sniffing and head and forepaw movements. Thus, TRH probably exerts a stimulatory action on central dopaminergic function, and it is likely that the effects of TRH on dopaminergic mechanisms in rat brain are similar to those in mouse brain. TRH releases dopamine in the nucleus accumbens [9,15], where there are TRH-containing fibers and TRH receptors [12,31], and does not release it in the caudate nucleus [9,15]. Furthermore, the drug elicits jumping behavior when combined with low doses of apomorphine in mice [34]. Since low doses of apomorphine preferentially activate the presynaptic inhibitory dopamine autoreceptors [3,28], this behavior involves, in part, the stimulation of presynaptic dopamine autoreceptors [34]. In addition to the inhibition of dopaminergic neurons by activating dopamine autoreceptors, the jumping behavior involves cholinergic inhibition, serotonergic inhibition, or GABAergic activation [34,36]. From the results, it is suggested that the jumping behavior could be opposing the locomotor stimulation via the same pathway in the nucleus accumbens [14,36]. Furthermore, long-term daily administration of TRH enhances locomotion and stereotyped behavior in animals, presumably by increasing the synthesis and release of dopamine [1, 26, 32, 35].

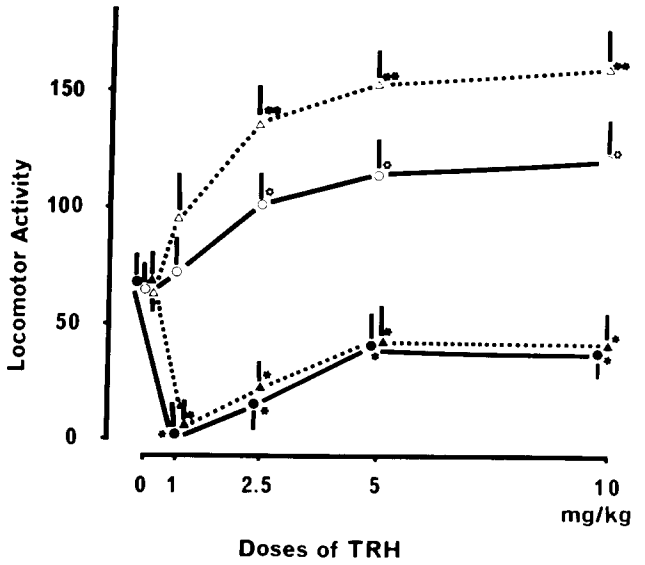

FIG. 1. Dose-response of locomotor activity induced by TRH and the inhibitory effects of haloperidol on TRH-induced hyperlocomotion. Mice received TRH ranging from 1 to 10 mg/kg SC for 1 and 21 days. Haloperidol (0.5 mg/kg SC) or saline was administered 25 min before the 1st or 21st TRH administration. Each value shows the mean±S.E. from 10 mice. (○) 1st TRH + Saline, (●) 1st TRH + Haloperidol, (△) 21st TRH + Saline, (▲) 21st TRH + Haloperidol. *$p<0.001$; significant difference from the respective saline + TRH, **$p<0.05$; significant difference from 1st TRH + Saline and ☆$p<0.05$; significant difference from respective Saline + Saline, determined by ANOVA and subsequent Tukey tests.

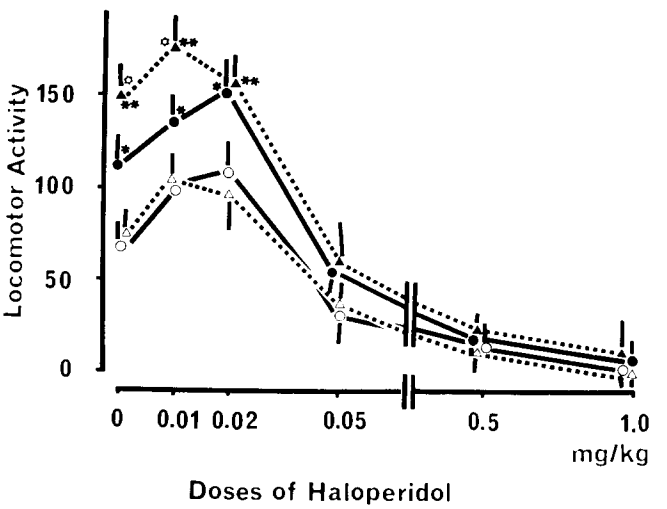

FIG. 2. Effect of haloperidol on hyperlocomotion induced by TRH. Mice received TRH (10 mg/kg SC) for 1 and 21 days. Haloperidol ranging from 0.01 to 1 mg/kg SC was administered 25 min before TRH or saline on the 1st and 21st day after daily administration of TRH to mice, and locomotor activity was measured 5 min later after TRH or saline. Each value indicates the mean±S.E. from 10 mice. (○) 1st Saline + Haloperidol, (●) 1st TRH + Haloperidol, (△) 21st Saline + Haloperidol, (▲) 21st TRH + Haloperidol. *$p<0.05$, **$p<0.01$; significant difference from respective control in the absence of TRH (Saline + Haloperidol) and ☆$p<0.05$; significant difference from 1st TRH + Haloperidol, determined by ANOVA and subsequent Tukey tests.

It is known that the long-term treatment with dopamine-mimetic drugs can result in progressively augmented or tolerant responses to these drugs. For example, repeated administration of amphetamine results in an increased sensitivity to the effect of the drug on spontaneous motor activity and stereotypy [16, 24, 29]. However, tolerance develops to the anorexigenic [18] and convulsive-threshold-lowering actions [7] of amphetamine. Furthermore, long-term administration of dopamine mimetic drugs [21,25] also enhances catalepsy, a behavior generally associated with reduced dopamine function. This may suggest, paradoxically, that the dopaminergic system may not become supersensitive but rather subsensitive during such long-term treatment. The present study examined whether or not acute and chronic effects of TRH, which may also act through dopaminergic mechanisms, would induce an increase in locomotion and a change in the frequency of jumping behavior.

METHOD

Animals

Healthy ddY male albino mice (25–30 g), purchased from Kyudo Animal laboratory (Kumamoto, Japan), were permitted food (CE-2, Clea Ltd. Japan) and water ad lib except during trials. All trials and breeding were carried out at an environmental temperature of 23±1°C with a 12 hr light-dark cycle. All experiments were carried out at 1000–1600 hr.

Measurement of Locomotion

Locomotor activity was measured as ambulation using an open-field apparatus. The open-field chamber was 60 cm in diameter and 50 cm in height and the floor was divided into 19 segments. Immediately after the animal was left in the apparatus, the number of segments on the floor traversed by the mouse was recorded during a 3 min period. Mice were divided into groups of 10 with equivalent ambulation scores as measured prior to the experiments. Ambulation was observed 5 min after TRH or saline on the 1st and 21st day during the course of daily drug administration.

Measurement of Jumping

As previously described [6,34], groups of five mice were simultaneously placed at the center of an octagonal platform of opaque plastic, 32 cm in diameter and 35 cm in height. When mice jumped off the platform or jumped 7 cm or more above it, this behavior was evaluated as a positive response. After subcutaneous (SC) injection of TRH, jumps were counted for 40 min.

Measurement of Body Weight

The body weight of the mice was measured every day for 21 days.

Long-Term Administration of TRH

TRH (10 mg/kg) was injected SC once per day at 1000 hr for 21 days. In the control group, saline was injected at a volume of 1 ml/kg for 21 days.

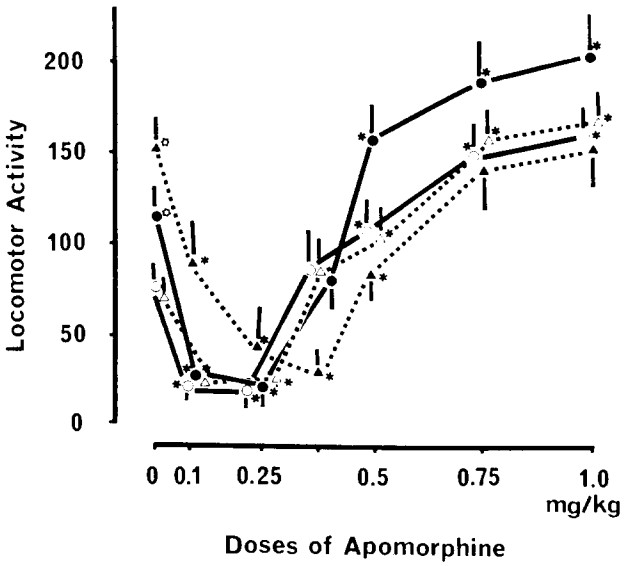

FIG. 3. Effect of apomorphine on hyperlocomotion induced by TRH. Mice received TRH (10 mg/kg SC) for 1 and 21 days. Apomorphine ranging from 0.1 to 1 mg/kg SC was administered 10 min before TRH or saline on the 1st and 21st day after daily administration of TRH to mice, and locomotor activity was measured 5 min later after TRH or saline. Each value indicates the mean±S.E. from 10 mice. (○) 1st Saline + Apomorphine, (●) 1st TRH + Apomorphine, (△) 21st Saline + Apomorphine, (▲) 21st TRH + Apomorphine. *$p<0.05$; significant difference from respective control in the absence of apomorphine (0 point), ☆$p<0.05$; from 1st Saline + Saline and 21st Saline + Saline, determined by ANOVA and subsequent Tukey tests.

Drug Interaction Study

To study the influence of apomorphine or haloperidol on TRH-induced hyperlocomotion, apomorphine (0.1–1 mg/kg) or haloperidol (0.01–1 mg/kg) was administered SC 10 min or 25 min before TRH (1–10 mg/kg) or saline on the 1st and 21st day after daily administration to mice, and locomotor activity was measured 5 min later after TRH or saline.

In order to evaluate jumping behavior on the 1st and 21st days of daily administration, the mice received TRH (1–20 mg/kg) 5 min after apomorphine (0.1–1 mg/kg) and jumping behavior was assessed immediately after TRH. These behaviors were counted for each rat manually by each observer who was blind to the allocated treatment. All experiments were performed at 1000–1600 hr.

Drugs

The drugs used were TRH (L-pyroglutamyl-L-histidyl-L-prolineamide L-tartrate monohydrate, Takeda, Osaka, Japan), apomorphine hydrochloride (Sandoz AG, Basel) and haloperidol hydrochloride (gift from Dainippon, Osaka, Japan). These drugs were dissolved in saline and injected SC at a volume of 1 ml/kg. Saline was given as the control.

Statistical Analysis

Statistical analyses were performed using ANOVA and subsequent Tukey tests for locomotor activity and body weight, and the two-tailed Mann-Whitney U-test for jumping behavior [30]. The level of significance chosen was $p<0.05$.

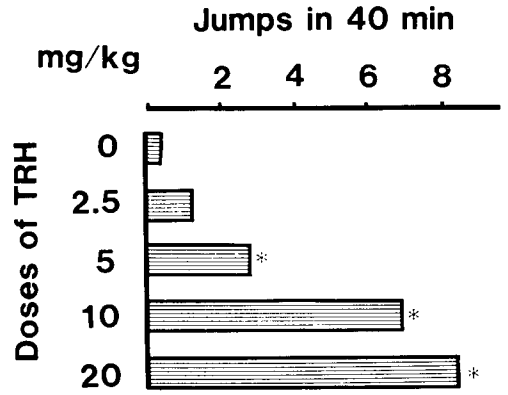

FIG. 4. Dose-responses in jumping to TRH. A single dose of TRH (2.5–20 mg/kg SC) was administered 5 min after apomorphine (0.25 mg/kg SC). *$p<0.002$; significance from the saline-injected group, determined by the Mann-Whitney U-test.

RESULTS

Effect of TRH on Locomotor Activity

Locomotor activity increased in a dose-dependent manner, 5–15 min following a single injection of TRH (1–10 mg/kg SC) (Fig. 1). Mild tremor, piloerection and salivation were evident at 10 mg/kg of TRH.

Following daily administration of TRH (1–10 mg/kg SC) for 21 days, the stimulatory effect of TRH on ambulation increased (Fig. 1). When mice were housed in home cages in groups of ten, they displayed sexual behaviors such as penile erection and mounting behavior during the period of daily administrations of TRH. Tremors, piloerection and salivation diminished at this stage.

Effect of Apomorphine and Haloperidol on TRH-Induced Hyperlocomotion

As shown in Fig. 2, the hyperlocomotion produced 5 min after a single administration of TRH (10 mg/kg) was potentiated by low doses of haloperidol (0.01–0.02 mg/kg SC) but was inhibited by higher doses of haloperidol (0.05–1 mg/kg SC). The inhibitory effect of haloperidol (0.5 mg/kg) on responses induced by TRH (1–10 mg/kg) was observed at all doses of TRH (Fig. 1). The hyperlocomotion induced by TRH (10 mg/kg) was inhibited by pretreatment with lower doses of apomorphine (0.1–0.25 mg/kg SC), whereas the hyperlocomotion appeared to increase with higher doses of apomorphine (0.5–1 mg/kg SC), but similar activities at 0 and 1 mg/kg were observed (Fig. 3).

Lower doses of haloperidol (0.01–0.02 mg/kg) potentiated the locomotion induced by repeated TRH, whereas the higher doses of haloperidol (0.05–1 mg/kg) inhibited locomotion (Figs. 1, 2). The inhibitory effect of low doses of apomorphine on the hyperlocomotion induced by daily administration of TRH (10 mg/kg) for 21 days was shifted from doses of 0.1–0.25 mg/kg for acute TRH (10 mg/kg) to 0.25–0.35 mg/kg in the chronic situation. The marked increase in locomotor activity by apomorphine (0.5–1 mg/kg) was attenuated to the levels of saline-injected groups, although the locomotor activity had already increased following daily treatment with TRH (Fig. 3).

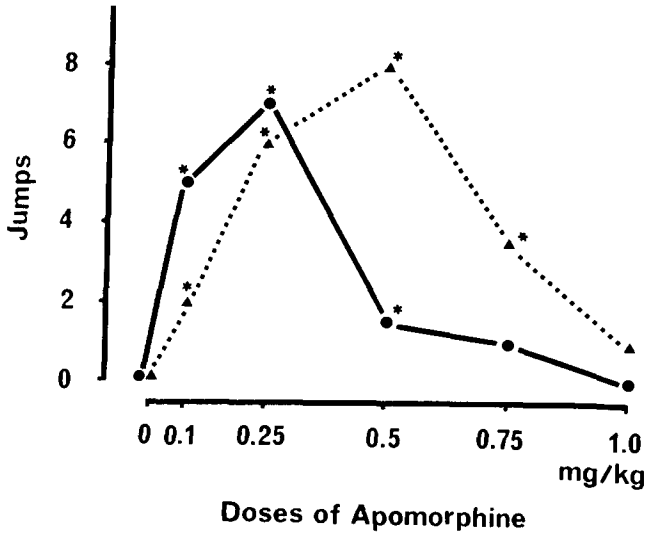

FIG. 5. Dose-responses of jumping in response to apomorphine. Mice received TRH (10 mg/kg SC) for 1 and 21 days. Apomorphine (0.1–1 mg/kg SC) was administered 5 min before the 1st and 21st dose of TRH. Each value shows the mean number of jumps from 10 mice. (●) 1st TRH + Apomorphine, (▲) 21st TRH + Apomorphine. *$p<0.002$; significant difference from the 1st TRH + Saline or 21st TRH + Saline, respectively, determined by ANOVA and subsequent Mann-Whitney U-test.

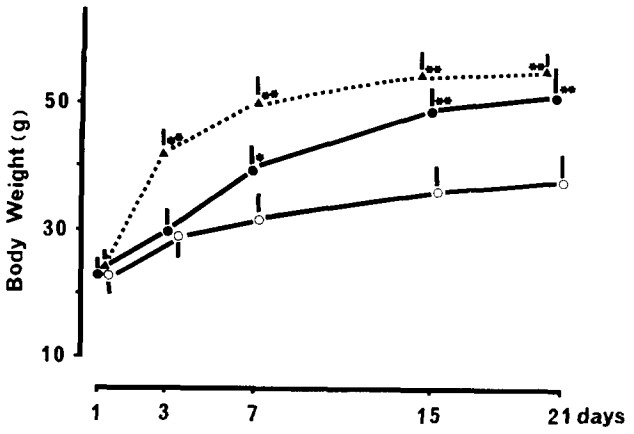

FIG. 6. Effect of long-term treatment with TRH on body weight in mice. (○) Saline 1 ml/kg, (●) TRH 2.5 mg/kg, (▲) TRH 10 mg/kg. *$p<0.05$, **$p<0.01$; significant difference from saline-injected group, determined by ANOVA and subsequent Tukey tests.

Effects of Acute and Repeated TRH on Jumping Behavior Induced by Combined Treatment With TRH and Apomorphine

TRH (2.5–20 mg/kg) or apomorphine (0.1–1 mg/kg) alone did not produce jumping, however when TRH was administered following apomorphine, jumping occurred, accompanied by hyperlocomotion. Jumping began within approximately 5 min of TRH administration and was most prominent for 10–20 min after TRH; it usually ceased within 30 min. After 30 min, the mice were markedly depressed. Tremor, piloerection and salivation also appeared approximately 20 min after TRH. The frequency of jumping was proportional to the dose of TRH (2.5–20 mg/kg) (Fig. 4); in contrast, jumping exhibited a bell-shape response curve with increasing doses of apomorphine (0.1–1.0 mg/kg) (Fig. 5).

As shown in Fig. 5, daily treatment with TRH (10 mg/kg) for 21 days also produced jumping behavior induced by concomitant treatment with apomorphine. In addition, the dose-response curve of apomorphine effects on jumping behavior was shifted to the right. Both TRH (5 and 10 mg/kg) treated groups of rats gained weight at greater rates than the saline-treated rats (Fig. 6).

DISCUSSION

Several studies have indicated that TRH can increase locomotor activity in rats [9,20] and mice [33,35]. Costall *et al.* (1979) [4], however, failed to find this behavior when TRH was injected into a variety of discrete brain regions in rats. Furthermore, there is evidence that TRH increases locomotor activity in rats after injection into the nucleus accumbens [9,20] and into the hypothalamus [19]. The reasons for this discrepancy are not clear. Recently, it has been reported that bilateral injection of potent TRH analogs such as CG-3509 and CG-3703 into the nucleus accumbens produce long-acting dopamine-like behavioral changes which are inhibited by haloperidol [10]. MK-771, a TRH analog, also produced a marked increase in dopamine synthesis and release as shown by a rise in tyrosine hydroxylase activity and homovanillic acid levels in the striatum and olfactory tubercle [27]. Considered together, these results suggest that the behavioral stimulant effects of TRH are mediated by the activation of dopaminergic neurons.

In this study, subcutaneous injection of TRH (1–10 mg/kg) produced an initial excitation of locomotion in mice, as previously reported [33]. When TRH was administered in combination with low doses of apomorphine (0.1–0.25 mg/kg), which stimulates presynaptic inhibitory dopamine autoreceptors [3,28], TRH-induced hyperlocomotion was depressed but jumping behavior occurred. The jumping behavior was proportional to the doses of TRH but showed an inverted-U relationship between jumping and dose of apomorphine. The activation of presynaptic dopamine autoreceptors may be involved in jumping behavior, whereas that of postsynaptic receptors may attenuate this behavior. At higher doses of apomorphine, TRH-induced hyperlocomotion increased in proportion to the doses of apomorphine. Since this increase occurred in an additive fashion, it appears that the activity of postsynaptic dopamine receptors is unaffected by acute TRH treatment.

Daily treatment with TRH (1–10 mg/kg) in mice induced a progressive increase in locomotion, in agreement with previously reported data [35]. After repeated treatment with TRH, the hyperlocomotion was increased by low doses of haloperidol (0.01–0.02 mg/kg) which preferentially blocks dopamine autoreceptors [11]. At the same time, the behavior was not modified by a high dose of haloperidol (0.5 mg/kg), which suggests that the affinity of haloperidol to the postsynaptic dopamine receptor may be more potent rather than that of released endogenous dopamine. Although the hyperlocomotion induced by a single injection of TRH was markedly inhibited at doses of 0.1–0.25 mg/kg of apomorphine, that induced by chronic TRH was also inhibited at doses at 0.25–0.35 mg/kg. Since the stimulatory effect of low doses of haloperidol and the inhibitory effect of low doses of apomorphine on hyperlocomotion tended to be shifted to the left and right, respectively, we conclude that presynaptic dopamine autoreceptor activity may be attenuated, and as

previously mentioned [1,26], release of dopamine at nerve terminals may be accelerated after repeated treatment with TRH. At high doses of apomorphine, repeated TRH did not produce an additive increase in locomotion, which was observed with acute TRH, suggesting that the sensitivity of postsynaptic dopamine receptors was attenuated following repeated TRH. Furthermore, combined treatment with chronic TRH (10 mg/kg) and apomorphine also produced jumping behavior; however, the dose response curve of apomorphine's effect on jumping behavior was shifted to the right. It is suggested that both pre- and postsynaptic dopamine receptors are attenuated following repeated TRH. Previous reports have also shown that after repeated treatment with TRH, the hyperlocomotion elicited by methamphetamine, a catecholamine releaser, is increased, while that induced by apomorphine is either nor altered or is decreased [35]. Thus, the sensitivity of dopamine receptors might be decreased following long-term administration of TRH. There is evidence suggesting that dopamine agonists preferentially act on presynaptic autoreceptors [3,28] and long-term dopamine mimetics result in the reduced ^{3}H-apomorphine binding which signifies fewer presynaptic receptors [21]. The inhibition of presynaptic dopamine autoreceptor activity by long-term treatment with TRH may be relatively more potent than the inhibition of postsynaptic receptors. It is suggested that since the number of postsynaptic dopamine receptors might correspond to dopamine released from presynaptic sites, repeated treatment with TRH in mice could produce enhancement of locomotor activity.

Previous studies have reported markedly enhanced dopamine function in thyrotoxic animals [8,17]. Nemeroff *et al.* [22] has reported significant hypothyroidism (decreases in serum TSH, T_3 and T_4) after chronic TRH administration. Accordingly, these observed effects may simply be due to alteration in thyroid function and bear no relationship to direct interaction of TRH with dopamine receptors. Furthermore, the normally nocturnal portion of the mouse light-dark cycle and TRH might simply be producing insomnia, i.e., the animals treated with TRH merely do not go to sleep, resulting in the appearance of increased locomotor activity.

In this study, increases in body weight and sexual behavior also appeared after repeated TRH. Such effects might be due to hormonal changes induced by repeated TRH, however, the mechanisms involved are not presently known.

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