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Effects of TA-0910, a novel orally active thyrotropin-releasing hormone analog, on the gait of ataxic animals

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Abstract

The effects of TA-0910 (1-methyl-(*S*)-4,5-dihydroorotyl-L-histidyl-L-prolinamide), a new thyrotropin-releasing hormone (TRH: L-pyroglutamyl-L-histidyl-L-prolinamide) analog, on ataxia were compared with those of TRH given by oral administration. The ataxic models used were the Rolling mouse Nagoya (RMN) showing genetic dysfunction of the cerebellum and striatum, rats with chemical degeneration of the inferior olive induced by 3-acetylpyridine (3-AP, 40 mg/kg, i.p.) and rats with a lesion of the thoracic spinal cord induced by mechanical compression. TA-0910 (1, 3, 10 mg/kg per day) clearly showed ameliorating effects on all these ataxic models. The dose-dependent effect of TA-0910 (10 mg/kg per day) on the gait of RMN was sustained until 2 weeks after the end of its 2-week administration. TRH (100, 300 mg/kg per day) also showed ameliorating effects on ataxia in RMN and 3-AP-treated rats. The ameliorating action of TA-0910 on ataxia was 100–300 times more potent than that of TRH.

Keywords: TRH (thyrotropin-releasing hormone); TA-0910 (TRH analog); Oral administration; Ataxia

1. Introduction

Thyrotropin-releasing hormone (TRH: L-pyroglutamyl-L-histidyl-L-prolinamide) is distributed in many parts of the central nervous system (CNS) (Kardon et al., 1977; Oliver et al., 1974), and has been shown to exert several CNS actions, such as an increase in locomotor activity, antagonism of reserpine-induced hypothermia and antagonism of pentobarbital-induced sleep (Horita et al., 1986). Moreover, TRH is reported to ameliorate the ataxic gait of mutant mice (Kurihara et al., 1985), accelerate recovery from the spinal injury induced by physical impact on the spinal cord in cats (Faden et al., 1981, 1984) and also improve the motor and sensory deficits associated with a spinal injury induced by transient compression of the spinal cord in rats (Hashimoto and Fukuda, 1990).

Many reports have shown that TRH exerts an ameliorating effect on ataxic symptoms in patients with amyotrophic lateral sclerosis and spinocerebellar degeneration (Brooks, 1989; Sobue et al., 1986). However, the therapeutic effect of TRH is very short-lived, because exogenously administered TRH is rapidly metabolized (Bassiri and Utiger, 1973). Furthermore, TRH has its endocrine action at much lower doses than those producing pharmacological actions on the CNS. Therefore, therapeutic agents for these diseases with a more long-lasting CNS activity and a lower endocrine potency than TRH are needed (Metcalf, 1982).

TA-0910 (1-methyl-(*S*)-4,5-dihydroorotyl-L-histidyl-L-prolinamide), a new TRH analog, has various CNS activities such as antagonism of pentobarbital-induced sleep, increase in spontaneous motor activity and antagonism of reserpine-induced hypothermia, each 10 times stronger than TRH on intravenous administration, 100 times stronger than TRH on oral administration and about 8 times more longer-acting than TRH (Yamamura et al., 1990; Yamamura et al., 1991a, b). Moreover, the thyrotropin-releasing activity of TA-0910 is 30 times weaker than that of TRH (Suzuki et al., 1990).

The aim of the present study is to examine the effects of TA-0910 on experimental ataxia in comparison with those of TRH. The ataxic models used were the Rolling mouse Nagoya (RMN) as a cerebellar or

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striatal ataxic model, 3-acetylpyridine (3-AP)-treated rats as an inferior olive-cerebellar tract-lesioned model and spinal cord compressed rats as a mechanically lesioned model. In these ataxic models, intraperitoneally administered TRH has already been reported to ameliorate the ataxia or to accelerate recovery from the deficits (Kurihara et al., 1985; Kurahashi et al., 1986; Hashimoto and Fukuda, 1990). In the present study, therefore, the effects of orally administered TA-0910 and TRH on the above ataxic models were examined.

2. Materials and methods

2.1. Experiment 1: Rolling mouse Nagoya (RMN)

2.1.1. Animals

Thirty-three male and 33 female RMN (14.6–29.4 g, 6–8 weeks old) were used. Animals of both sexes had to be utilized to prepare a sufficient number of ataxic animals, because they reproduce poorly. We had previously observed that both sexes showed the same reaction to drug treatment (data not shown). They were bred by Marugo Research Service Co. (Saitama, Japan) and were housed in groups of two to five in plastic cages (42W × 26D × 15H cm). The animals were kept in an air-conditioned room with controlled temperature (23 ± 1°C), humidity (55 ± 5%) and lighting (lights on 6:30 through 18:30). They were allowed free access to a standard pellet diet (CRF-1, Oriental Yeast Co.) and tap water.

2.1.2. Procedures

Each RMN was transferred to a plastic cage (42W × 26D × 15H cm) on an ANIMEX (sensitivity; 10 μA, FARAD ELECTRONICS), a locomotion counter based on the change in the current of the resonant coil circuit. The number of falls was counted visually and spontaneous motor activity was recorded on a digital counter. The number of falls and spontaneous motor activity were measured for 10 min immediately after transfer from the home cage. The index of ataxia was defined as the fall index (number of falls/spontaneous motor activity for 10 min).

The animals were divided evenly into six groups based on the fall index of individual animals. The drugs were administered orally once daily for 14 days. The fall index was measured 1, 3, 5, 7 and 24 h after the first dose, 1 h after drug administration on the 7th and 14th days of repeated administration period, and on the 7th, 14th and 21st days after drug withdrawal. The fall index after withdrawal was measured at about the same time (10:00–15:00) as during the administration period.

2.2. Experiment 2: 3-acetylpyridine-treated rats

2.2.1. Animals

Sixty-six male Wistar rats (Japan SLC; 250–304 g, 10 weeks old) were used. They were individually housed in the compartment (15W × 25D × 14H cm) of stainless steel five-compartment wire mesh cages (75W × 25D × 14H cm). Animal maintenance conditions were the same as described above.

2.2.2. Procedures

The rats were trained to run from one end to the other of the recording paper (width: 30 cm, length: 200 cm) after an electric shock (20 mA, 0.2 s, USA-200, Unique Medical) given via a clip electrode attached to the tail root. The ataxic parameters consisted of the speed of running over the entire length of the recording paper, mean step length and step angle measured from the footprints of the hind limbs on the whole length of recording paper (Fig. 2). The animals were evenly divided into seven groups based on the running speed. Out of seven groups, six groups were treated with 3-acetylpyridine (3-AP, 40 mg/kg, i.p.) and one remaining group was treated with 0.9% physiological saline as a control group. From the following day, at about 23 h after the 3-AP treatment, oral drug treatment was started and continued once daily for 22 days. Ataxic parameters were measured 1 h after drug administration on days 1, 2, 3, 5, 7, 9, 15 and 22.

2.3. Experiment 3: spinal cord-compressed rats

2.3.1. Animals

Seventy male Wistar rats (Clea Japan; 330–388 g, 12 weeks old) were used. They were individually housed in the compartment (15W × 25D × 14H cm) of stainless steel 5-compartment wire mesh cages (75W × 25D × 14H cm). Other maintenance conditions were the same as described above.

Table 1
Neurologic scores of spinal cord compression-induced ataxia in rats

Score	Neurologic symptoms
0	No spontaneous movement of the hind limbs and no withdrawal response to tail pinching, including avoidance movements by the fore limbs, biting of clamps, and vocalization
1	No spontaneous movement of the hind limbs, but showing withdrawal response to tail pinching, including avoidance movements by the fore limbs, biting of clamps, and vocalization
2	Barely perceptible coordinated movement of the hind limbs and fore limbs
3	Well coordinated movement of the hind and fore limbs
4	Able to walk with weight bearing by all four limbs but with an ataxic gait
5	Normal walking

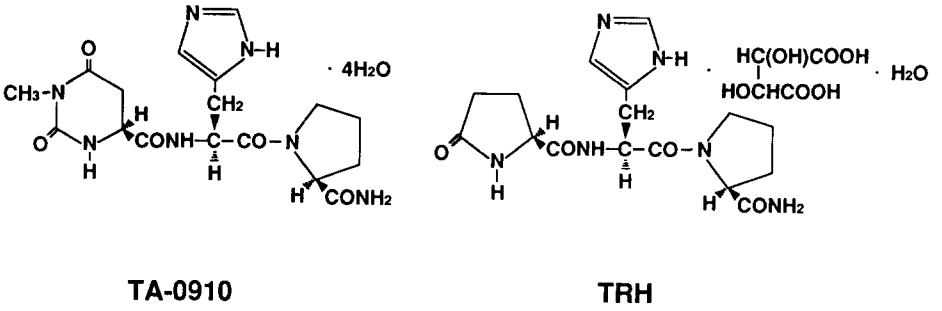

Fig. 1. Chemical structures of TA-0910 and TRH.

2.3.2. Procedures

The experiment was performed according to Hashimoto and Fukuda's method (Hashimoto and Fukuda, 1990).

After exposure of the dorsal part of the spinal column at the twelfth thoracic vertebral level (T_{12}) under pentobarbital-Na (60 mg/kg, i.p.) anesthesia, a small burr hole was made at the center of the dissected surface of the vertebra. A stainless steel screw (2 mm in diameter and 5 mm in length) was implanted into the burr hole made just above the dura mater, and then the incision was sutured. On the following day, under ether anesthesia, the suture was cut to expose the head of the screw, and the spinal cord was compressed by inserting the screw as far as possible. The screw was left in place for 30 min. Following the removal of the screw, the incision was resutured.

The neurologic symptom produced by spinal cord compression was evaluated according to Hashimoto and Fukuda's neurologic scores (Table 1). Rats with a score of 1 and 2 24 h after spinal cord compression were divided evenly into six groups based on the neurologic scores and rats with a score 3 were discarded. Neurologic symptoms were scored 24 h and 2, 3, 5, 7, 10, 14, 21, 28, 35 and 42 days after removal of the screw. The animals started receiving oral treatment with drugs 24 h after spinal cord compression. The

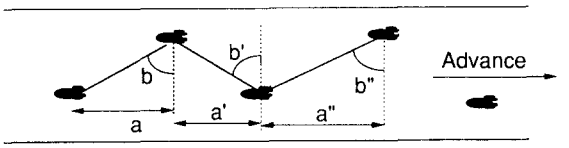

Fig. 2. Gait parameters from footprints of the hind limbs. All step angles and step lengths of the whole length of recording paper were measured, and their means were computed. a, a', a": step length. b, b', b": step angle.

treatment was continued once daily immediately after each neurologic scoring for 41 days.

2.4. Drugs and treatment

TA-0910 (1-methyl-(*S*)-4,5-dihydroorotyl-L-histidyl-L-prolinamide tetrahydrate: Lot No. 703010) and TRH (L-pyroglutamyl-L-histidyl-L-prolinamide L-tartrate monohydrate: Lot No. 1221140A) were synthesized in the Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co. Their chemical structures are shown in Fig. 1. Other drugs used were 3-acetylpyridine (Aldrich), pentobarbital-Na (Nacalai tesque), and diethyl ether (Katayama Chemical). TA-0910 (1, 3 and 10 mg/kg, p.o.) and TRH (100 and 300 mg/kg, p.o.) were dissolved in distilled water. 3-Acetylpyridine and pentobarbital-Na were dissolved in 0.9% physiological

Table 2
Effects of TA-0910 and TRH (p.o.) on the number of falls and spontaneous motor activity in RMN

Drug	Dose	*n*	Spontaneous motor activity (counts/10 min ± S.E.)		No. of falls (counts/10 min ± S.E.)	
			Pre	Post	Pre	Post
Saline		11	52.9 ± 12.8	57.8 ± 12.1	22.1 ± 5.7	22.6 ± 5.1
TA-0910	1	11	56.5 ± 16.4	88.8 ± 22.7	18.7 ± 3.3	19.3 ± 4.4
	3	11	58.1 ± 12.8	95.8 ± 20.4	22.1 ± 5.8	21.0 ± 6.8
	10	11	83.2 ± 23.9	102.4 ± 31.7	34.6 ± 11.5	16.9 ± 7.0 [a]
TRH	100	11	63.7 ± 14.2	64.7 ± 11.4	23.5 ± 5.0	22.1 ± 4.5
	300	11	90.5 ± 17.7	95.5 ± 25.7	30.6 ± 6.0	25.0 ± 5.5

Pre- and post-drug values were measured 24 h before and 1 h after the drug administration, respectively. [a] $P < 0.05$ compared with the pre-drug value (paired t-test).

saline (Otsuka). All drugs were dissolved immediately before use and administered in volumes of 10 and 2 ml/kg to RMN and rats, respectively.

2.5. Statistical analysis

All data were expressed as the means ± S.E. The data obtained from Experiment 1 and 2 were analyzed by analysis of variance (ANOVA) for repeated measurements, followed by Dunnett's or Scheffé's multiple comparison test. Comparison between the pre- and post-treatment values of the number of falls and spontaneous motor activity in RMN was carried out by the paired *t*-test. Comparison of ataxic parameters between the 3-acetylpyridine-treated and non-treated rat groups was also performed by Mann-Whitney's U-test. The data obtained from experiment 3 were also expressed as the means ± S.E. to make the evaluation of the drug effects easier and analyzed by the Kruskal-Wallis test, followed by the Scheffé type multiple comparison test. The differences were considered to be statistically significant when the P value was less than 0.05.

3. Results

3.1. Experiment 1: Rolling mouse Nagoya (RMN)

In the experimental cage, RMN showed reeling with an ataxic gait mainly of the hind limbs and sometimes rolling. At 24 h before the first drug dose, the mean number of falls, spontaneous motor activity and fall index during the 10 min period were 18.7–34.6 counts, 52.9–90.5 counts and 0.395–0.421, respectively (Table 2, Fig. 3), and there were no significant differences in these pre-treatment values among the groups.

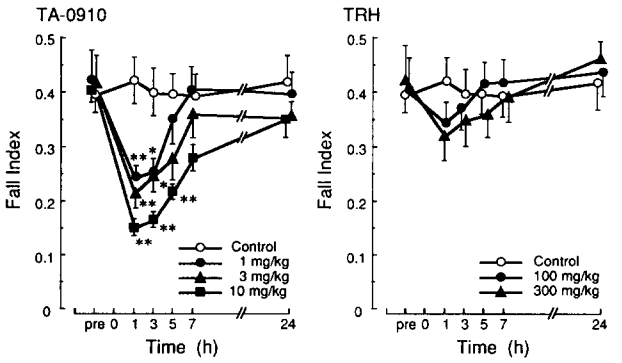

Fig. 3. Effects of single administration (p.o.) of TA-0910 and TRH on the fall index (number of falls/spontaneous motor activity in 10 min) in RMN ($n = 11$). Drugs were administered 1 h before placing the animal in the cage on an ANIMEX for measurements. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with control (ANOVA followed by Dunnett's multiple comparison test).

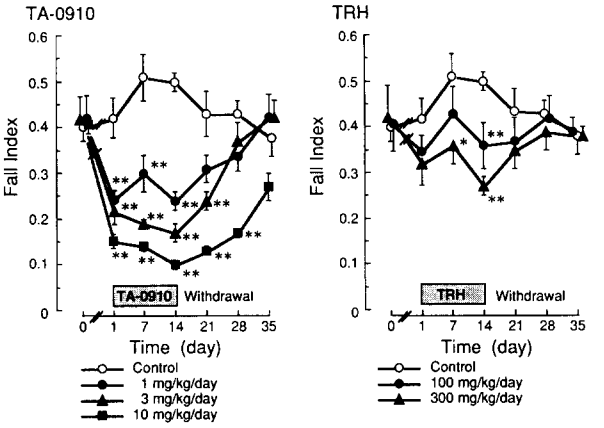

Fig. 4. Effects of chronic administration (once daily, p.o.) and withdrawal of TA-0910 and TRH on the fall index (number of falls/spontaneous motor activity in 10 min) in RMN ($n = 11$). Drugs were administered 1 hr before the start of measurements during the administration period. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with control (ANOVA followed by Dunnett's multiple comparison test).

When spontaneous motor activity and the number of falls 1 h after the first dose were compared with the pre-treatment values in each group, spontaneous motor activity in the TA-0910-treated groups tended to increase, but these increases were statistically insignificant. TA-0910 at the dose of 10 mg/kg significantly decreased the number of falls (Table 2).

After the first dose, TA-0910 decreased the fall index dose dependently and the decreases at all doses were statistically significant (Fig. 3). The peak effect was observed 1 h after administration. Thereafter, the effect of TA-0910 at the dose of 10 mg/kg was still significant at 5 h, but disappeared within 24 h after the first dose. TRH at the doses of 100 and 300 mg/kg tended to lower the fall index from 1 to 3 h after administration, although the decreases were not significant (Fig. 3).

On the 7th and 14th days of repeated administration, TA-0910 at the doses of 1, 3 and 10 mg/kg per day significantly and dose dependently decreased the fall index (Fig. 4). The fall index at the highest dose remained significantly depressed until 14 days after drug withdrawal. TRH at the doses of 100 and 300 mg/kg per day also depressed the fall index slightly and the effect was significant on the 7th or 14th day of chronic administration (Fig. 4), but it disappeared by the 7th day after withdrawal.

During any observation period, significant differences in spontaneous motor activity from the control group were not observed among the drug-treated groups (data not shown).

3.2. Experiment 2: 3-AP-treated rats

Twenty-four hours after treatment with 3-AP, the rats demonstrated the ataxic gait called 'mud-walking'

(Llinas et al., 1979) accompanied by marked decreases in the running speed, step length and step angle compared with those of the non-treated rats. These gait changes of the 3-AP-treated rats were sustained during the experimental period of 22 days (Fig. 5).

TA-0910 at the doses of 3 or 10 mg/kg per day moderately but significantly increased the running speed on the 22nd day and the step length from the 15th day of drug treatment, and markedly increased the step angle on the 22nd day (Fig. 5). TRH at the dose of 300 mg/kg per day significantly increased the running speed on the 15th day, the step length from the 7th day onward and the step angle on the 22nd day (Fig. 5).

3.3. Experiment 3: spinal cord-compressed rats

Twenty-four hours after spinal cord compression, the rats demonstrated ataxia in the lower part of the body, mainly of the hind limbs. The mean initial neurologic score of each group was 1.4–1.5 and it increased with time (Fig. 6). The mean neurologic scores in the control group 7, 14, 21, 28, 35 and 42 days after removal of the screw were 2.5, 3.3, 3.6, 4.0, 4.2 and 4.5, respectively. There were no significant differences in the score among the groups during the first 20 days, but the neurologic scores of the groups treated with TA-0910 at the dose of 3 and 10 mg/kg per day recovered more rapidly and were significantly higher

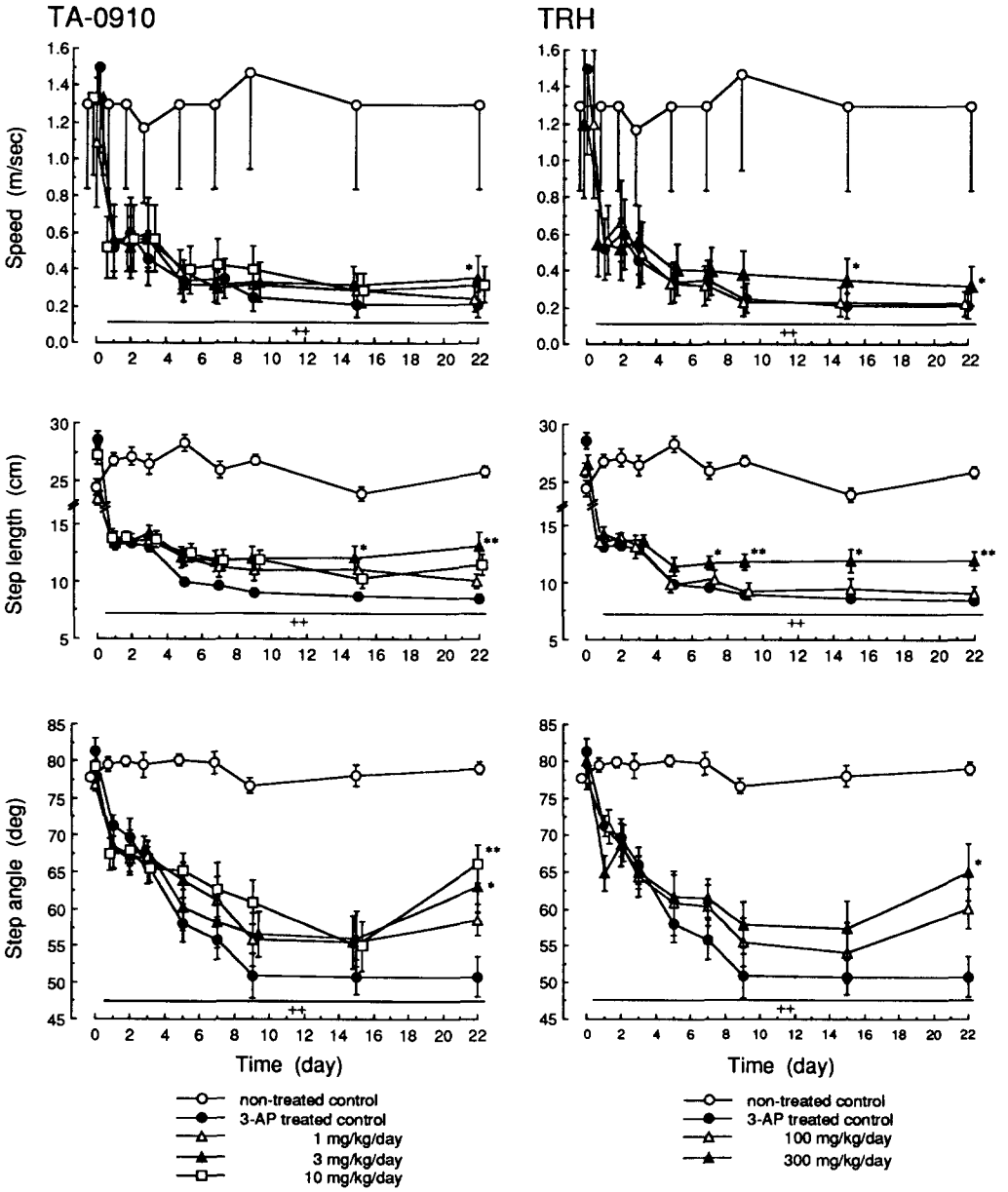

Fig. 5. Effects of chronic administration (once daily, p.o.) of TA-0910 and TRH on the ataxic parameters of 3-acetylpylidine (3-AP)-treated rats ($n = 8$–10). Drugs were administered 1 h before each measurement. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with 3-AP-treated control (ANOVA followed by Scheffé's multiple comparison test). $^{++}P < 0.01$ compared with the non-treated control (Mann-Whitney U-test).

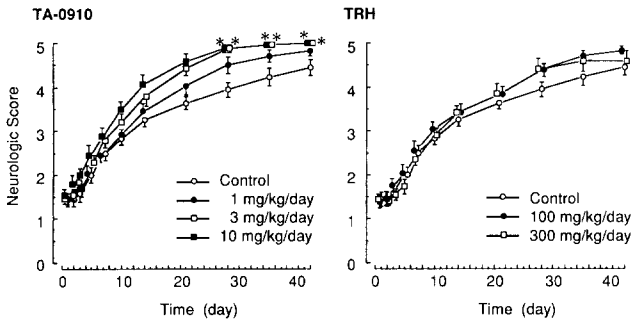

Fig. 6. Effects of chronic administration (once daily, p.o.) of TA-0910 and TRH on the neurologic score of spinal cord-compressed rats ($n = 11$–12). Drugs were administered daily immediately after each observation. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with the control (Kruskal-Wallis test followed by Scheffé's multiple comparison test).

than those of the control group for the last two weeks of the experimental period (Fig. 6). The mean neurologic scores of the group with TA-0910 at the dose of 10 mg/kg per day in 28, 35 and 42 days were 4.9, 5.0 and 5.0, respectively. The mean scores of the groups treated with TRH at the doses of 100 and 300 mg/kg per day increased nearly at the same rate as those of the control group during the entire experimental period (Fig. 6).

4. Discussion

RMN is a genetically ataxic model in which the hind limbs are mainly affected. Compared with the normal mouse, the cerebellum of RMN shows a decrease in the number of granule cells (Nishimura, 1975), a decreased size of the organ (Muramoto et al., 1982), and abnormal neurotransmitter levels (Muramoto et al., 1981). Recently, an abnormality of cerebral glucose utilization in the basal ganglia area in RMN was reported (Yamaguchi et al., 1992). These findings suggest that RMN is an ataxic model with abnormalities in the cerebellum and the basal ganglia.

In the present study, single administration of TA-0910 at the dose of 3 mg/kg or more markedly decreased the fall index, an index of ataxia. TA-0910 has been reported to increase spontaneous motor activity (Yamamura et al., 1990). In the present study, TA-0910 also showed a tendency to increase spontaneous motor activity. The number of falls was thought to increase with increasing spontaneous motor activity. The TA-0910-administered groups, however, did not show any increase in the number of falls. On the contrary, the group treated with the dose of 10 mg/kg showed a significant decrease in the number of falls. These results indicate that the decrease in the fall index produced by TA-0910 in RMN was not only due to an increase in spontaneous motor activity but also to an ameliorating action on ataxia.

The ameliorating action on ataxia of TA-0910 at the dose of 10 mg/kg was observed from 1 to 5 h after oral administration. Chronic administration of TA-0910 for 2 weeks produced an even more marked and clearly dose-dependent ameliorating action on ataxia in this disease model. Thus, its effect was not attenuated by repeated administration, suggesting that drug tolerance was not induced. The ameliorating effect of repeatedly administered TA-0910 at the dose of 10 mg/kg was maintained until 2 weeks after drug withdrawal. Though the reason for this long-lasting effect is not clear, such a continuous effect has been shown during a withdrawal period after chronic administration of TRH for 3 months in patients with spinocerebellar degeneration (Sobue et al., 1986).

Intraperitoneally administered TRH at the dose of 10 and 25 mg/kg has previously been reported to ameliorate the ataxia in RMN (Kurihara et al., 1985). In the present study, orally administered TRH at the dose of 100 and 300 mg/kg per day for 2 weeks significantly ameliorated the ataxia in RMN. Since high oral doses of TRH have been shown to cause some intestinal absorption of TRH into the blood (Yokohama et al., 1984), an ameliorating effect of TRH after chronic oral administration is understandable. However, the potency of TRH was much weaker than that of TA-0910: i.e., TA-0910 was shown to be 100 times more potent than TRH. In view of an increased level of noradrenaline in the cerebellum of RMN, the ameliorating action on ataxia of TRH has been suggested to be due to an acceleration of the turnover of noradrenaline in the cerebellum by this compound (Konagaya et al., 1980). TA-0910 has also been reported to have an accelerating action on noradrenaline turnover in rat brain (Fukuchi et al., 1991). Therefore, the ameliorating action of TA-0910 may be at least partly due to the same mechanism as that for TRH.

In 3-acetylpyridine-treated rats, the unique ataxia, so-called 'mud-walking', mainly involving the hind limbs (Llinas et al., 1979) was sustained for 43 days after the treatment with 3-AP (Sukin et al., 1987). From histological and electrophysiological observations, 3-AP-treated rats show degeneration of the inferior olive nucleus and dysfunction of the olivo-cerebellar tract (Llinas et al., 1979). From these reports, this model was thought to reflect ataxia caused by permanent dysfunction of the cerebellum from degeneration of the climbing fibers and could serve as a model of the olivo-ponto-cerebellar atrophy observed in spinocerebellar degeneration. In the present study, ataxia of this model clearly appeared in 24 h, gradually worsened until 7–9 days after the 3-AP treatment, and then became stable. In this model, an ameliorating effect of TA-0910 appeared in the later stable phase. However, the effect of TA-0910 did not appear during the pro-

gressive phase of ataxia, probably because its effect was masked by the progressing ataxia. Chronic treatment with TRH at the dose of 300 mg/kg per day also showed an ameliorating action on the ataxia. From their minimum effective doses, the effect of TA-0910 on this model was considered to be 100 times more potent than that of TRH.

The ameliorating mechanisms of TRH and TA-0910 are unclear. The single spike firing rate of the Purkinje cells in inferior olive-lesioned rats is reported to be significantly higher than that in intact rats (Savio and Tempia, 1985). Moreover, microiontophoretically applied TRH was reported to depress the activity of cerebellar cortex neurons (Renaud et al., 1975). In this model, therefore, the amelioration of ataxia by TRH and its analog, TA-0910, may partly be based on their depressing and normalizing action in cerebellar cortex neurons.

In contrast to the present result, Kurahashi et al. (1986) reported that TRH was not effective on the ataxia of 3-AP-treated rats. The model they used was, however, supposed to be more severe than the present model, because, at the dose of 70 mg/kg they used, intraperitoneally administered 3-AP caused degeneration of not only the inferior olive complex but also the nucleus ambiguus, the facial and hypoglossal nuclei (Desclin and Escubi, 1974).

The main signs of spinal compressed rats are transient motor and sensory dysfunction of the hind limbs. TA-0910 at the oral dose of 3 mg/kg or more showed a marked accelerating action on the recovery from the ataxia. Hashimoto et al. (1990) reported that the potency of TRH depended on the administration frequency at the same daily dose. This observation suggests that the potency of TRH depends on the durability of its blood and cerebrospinal fluid level. The half-life of intravenously administered TA-0910 at the dose of 1 mg/kg in cerebrospinal fluid is about 54 min, 3–5 times longer than that of TRH in rats (Furuuchi et al., unpublished data). From these observations, the potent ameliorating effect of TA-0910 on ataxia appears to be due to its greater stability in the living body compared with TRH.

In the present study, TRH orally administered at the dose of 300 mg/kg per day showed only a tendency to cause amelioration, probably because the ameliorating effect of orally administered TRH was too weak to exert its effect on the naturally recovering, transient spinal ataxia of this model. There have been reports that endogenous TRH levels are increased in the experimentally injured spinal cord (Faden et al., 1986; Salzman et al., 1987), that exogenously administered TRH decreases the neuronal loss induced by axotomy (Banda et al., 1987b) and that TRH accelerates neurite extension in cultured spinal ventral horn neurons (Banda et al., 1985; Banda et al., 1987a). TA-0910 has also recently been reported to have a neurotrophic factor-like action like that of TRH (Iwasaki et al., 1992). From these reports, the accelerating effect of TA-0910 on the functional recovery from spinal cord injury is partly derived from its neurotrophic factor-like action.

Recently, reports have accumulated that TRH has an ameliorating effect on the functional disorders of patients with amyotrophic lateral sclerosis or spinocerebellar degeneration (Brooks, 1989; Sobue et al., 1986). However, the therapeutic effect of TRH, produced only by intravenous or intramuscular administration, is weak and transient at best. Therefore, a new TRH analog with a more potent and longer-lasting efficacy has been awaited (Metcalf, 1982). The present study demonstrated that TA-0910 is an orally active anti-ataxic agent which is more potent and longer-acting than TRH and may prove to be useful in the treatment of the cerebellar and/or spinal functional disorders in patients with amyotrophic lateral sclerosis or spinocerebellar degeneration.

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