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Anti-ataxic effects of TRH and its analogue, TA-0910, in Rolling mouse Nagoya by metabolic normalization of the ventral tegmental area

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1 The mechanism of the anti-ataxic action of thyrotropin-releasing hormone (TRH) and its analogue, TA-0910, in the Rolling mouse Nagoya (RMN), an ataxic mutant mouse, has been investigated.

2 TRH (30 mg kg^{-1}, i.p.) and TA-0910 (3 mg kg^{-1}, i.p.) reduced the fall index (number of falls/spontaneous motor activity), an index of ataxia, 10-30 and 10-60 min after administration, respectively.

3 Relative local cerebral glucose utilization (LCGU) in the cerebellum and ventral tegmental area (VTA) of the rolling mouse was significantly smaller than that in normal animals. TRH (30 mg kg^{-1}, i.p.) and TA-0910 (3 mg kg^{-1}, i.p.) increased the relative LCGU value of the VTA but not of the cerebellum in rolling mice to the level of normal animals.

4 These results suggest that the ataxia of the rolling mouse may be due to dysfunction of the cerebellum and VTA, and that amelioration by TRH and TA-0910 could result from metabolic normalization of the VTA.

Keywords: Rolling mouse Nagoya (RMN); thyrotropin-releasing hormone (TRH); TA-0910; ataxia; local cerebral glucose utilization (LCGU); ventral tegmental area (VTA); cerebellum

Introduction

Thyrotropin-releasing hormone (TRH: L-pyroglutamyl-L-histidyl-L-prolinamide)-like immunoreactivity is present in various parts of the mammalian central nervous system (CNS) (Brownstein *et al.*, 1974; Oliver *et al.*, 1974; Kardon *et al.*, 1977). Apart from the thyroid stimulating hormone releasing action, this peptide exerts several CNS actions, such as an increase in locomotor activity and antagonism to pentobarbitone-induced sleep (Sharp *et al.*, 1984a,b). Furthermore, pharmacological studies revealed amelioration of ataxia by TRH in cytosine arabinoside-treated mice (Yamamoto & Shimizu, 1989) and spinal injured rats (Hashimoto & Fukuda, 1990). These suggest that TRH has a therapeutic potential in ataxic gait.

Rolling mouse Nagoya (RMN) has the rolling gene homogeneously (genotype, rol/rol) and show motor disturbances of the hind limbs, including falling and lurching on walking. In RMN (rol/rol), intraperitoneally administered TRH ameliorates the ataxic gait (Kurihara *et al.*, 1985; Mano *et al.*, 1986). We have also reported that TRH and a new TRH analogue, TA-0910 ((−)-*N*-[(S)-hexahydro-1-methyl-2,6-dioxo-4-pyrimidinylcarbonyl]-L-histidyl-L-prolinamide tetrahydrate), reduce the ataxia of the rolling mouse (Kinoshita *et al.*, 1995). However, the mechanism by which TRH and TA-0910 improve the abnormal gait in the rolling mouse remains unclear.

Local cerebral glucose utilization (LCGU) is a metabolic index of local neuronal activity (Sokoloff *et al.*, 1977). Decrease and increase of LCGU are correlated to the inhibition and excitation of activity *in vivo*, respectively (Kennedy *et al.*, 1975; Yarowsky *et al.*, 1983). In the present study, we measured the LCGU in various discrete regions of the brain to determine the sites for the mechanism of the anti-ataxic action of TRH and TA-0910 in the rolling mouse.

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Methods

Animals

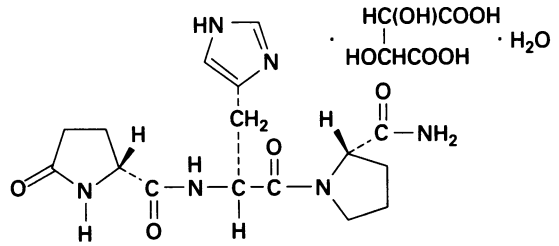
Forty-eight male rolling mice (RMN, rol/rol) (25-33 g, 6-8 months old) were used for the behavioural study. Eight male normal mice (RMN, +/+) (33-39 g, 6-8 months old) and 24 male rolling mice (RMN, rol/rol) (22-30 g, 6-8 months old) were used for the autoradiographic study. They were bred by Marugo Research Service Co., Ltd. (Saitama, Japan) and were housed in groups of 5-10 in plastic cages (42W × 26D × 15H cm). Animals were kept in an air-conditioned room with controlled temperature (23 ± 1°C), humidity (55 ± 5%), and 12 h lighting (lights on 06 h 30 min until 18 h 30 min) and were allowed free access to a standard pellet diet (CRF-1, Oriental Yeast Co., Ltd.) and tap water.

Drugs and treatment

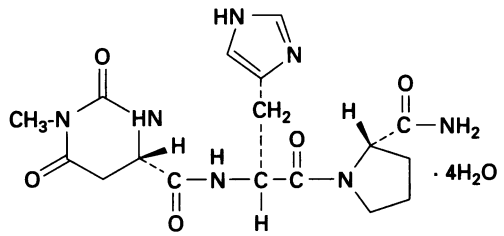
TRH tartrate (L-pyroglutamyl-L-histidyl-L-prolinamide L-tartrate monohydrate) and TA-0910 ((−)-*N*-[(*S*)-hexahydro-1-methyl-2,6-dioxo-4-pyrimidinylcarbonyl]-L-histidyl-L-prolinamide tetrahydrate) were synthesized in the Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd, Japan. Their chemical structures are shown in Figure 1. 2-Deoxy-D-[^{14}C]-glucose (2-DG, sp. act. 55 mCi $mmol^{-1}$) was purchased from Amersham. TRH (3, 30 mg kg^{-1}, i.p.), TA-0910 (0.3, 3 mg kg^{-1}, i.p.) and 2-DG (150μCi kg^{-1}, i.v.) were dissolved in physiological saline (0.9% NaCl sol., Otsuka Pharmaceutical Co., Ltd.) immediately before use, and administered in a volume of 10 ml kg^{-1} body weight. Other drugs used were carboxymethyl cellulose (WAKO), isopentane (nacalai tesque), haematoxylin (Merck) and eosin-G (Merck).

Behavioural study

Each of the rolling mice was transferred singly to a plastic cage (42W × 26D × 15H cm) on a locomotion counter with a multiple photo-cell sensor system (SCANETT: sensitivity; MV2 = 10, Toyo Sangyo Co., Ltd.). The number of falls was



TRH-tatrate



TA-0910

Figure 1 Chemical structures of TRH and TA-0910.

counted visually and spontaneous motor activity was recorded on a digital counter for 10 min immediately after transfer from the home cage. The index of ataxia (the fall index) was defined as the number of falls/spontaneous motor activity for 10 min.

The animals were divided into 5 similar groups of 9 or 10 mice based on the mean fall index of individual animals, which was obtained from three measurements made during 72–24 h before drug administration. The fall index was calculated at 10, 30, 60, 120 and 180 min and 24 h after drug administration.

All experimental data were collected under open conditions, and each animal was used only for one experiment.

Autoradiographic study

LCGU was measured by the 2-DG method (Sokoloff *et al.*, 1977). In the present study, we used relative LCGU instead of Sokoloff's absolute LCGU (Sharp *et al.*, 1983), because the mouse's lumped constant which is necessary to obtain the absolute LCGU and is a combination of six constants about the internal movement of 2-DG (Sokoloff *et al.*, 1977), was not known.

The animals were fasted for about 12 h before the experiment and were kept fully awake during the experiment. 2-DG (150 μCi kg^{-1}) was administered via the tail vein within 5 s. Immediately after the administration of 2-DG, drugs were administered intraperitoneally. Then, the animals were kept freely moving in an individual, semi-dark and quiet plastic cage (25W × 18D × 13H cm). Forty-five min after the 2-DG injection, the animals were decapitated. The brain was quickly removed from the skull, immersed in 3% carboxymethyl cellulose chilled with dry ice, frozen in isopentane chilled with liquid N_2 and stored at −80°C. The frozed brain was then serially sectioned (sections 20 μm thick) in a coronal plane with a cryostat (1720 DIGITAL, Leitz). At every 9 slices (180 μm) three sections were taken on a slide glass, and dried immediately at 50°C. These sections were kept in contact with X-ray films (SB-5, Kodak) together with calibrated ^{14}C standards (ARC) for 7–8 days at 4°C in light-tight X-ray cassettes, after which the films were developed. The sections corresponding to the autoradiographs were stained with haematoxylin-eosin for histological confirmation of the brain structures.

The density of grains in 32 gray matter structures and 1 white matter structure (corpus callosum) was determined with a colour image analyzing system (MCID-system, Imaging Research Inc.). The radioisotope level of each structure was calculated from the level of the ^{14}C standard. A particular structure was selected in at least 5 different areas from 3–6 neighbouring sections, and the radioisotope level was averaged. Then, the relative LCGU value of each gray matter structure was normalized using the radioisotope level of corpus callosum as a standard (1.00).

Statistical analysis

All data are expressed as the mean ± s.e.mean. The data from the behavioural study were analyzed by analysis of variance (ANOVA) for repeated measurements, followed by Duncan's multiple range test. The data from the autoradiographic study were analyzed by ANOVA, followed by the multiple t test.

Results

Behavioural study

When placed in the experimental cage on a SCANETT, RMN showed a reeling motion with an ataxic gait of the hind limbs and sometimes rolled over. The mean values of spontaneous motor activity, number of falls and fall index of each group in the 10 min pre-drug period were 221.4–285.1, 15.8–20.9 and 0.067–0.078, respectively (n = 9–10). There were no significant differences in these pre-treatment values among the groups (Table 1 and Figure 2).

TRH at a dose of 30 mg kg^{-1} markedly lowered the fall index at 10 and 30 min after the injection, and the peak effect was observed 10 min after the injection ($F_{4,43}$ = 11.879, P < 0.01 at 10 min and $F_{4,43}$ = 7.697, P < 0.05 at 30 min; Duncan's multiple range test; Figure 2). Thereafter, the effect of TRH declined and disappeared within 60 min.

TA-0910 at a dose of 3 mg kg^{-1} significantly decreased the fall index 10, 30 and 60 min after the injection ($F_{4,43}$ = 11.879, $F_{4,43}$ = 7.697 and $F_{4,43}$ = 4.832, respectively. P < 0.01 at 10, 30 and 60 min; Duncan's multiple range test; Figure 2). The effect of TA-0910 at a dose of 3 mg kg^{-1} lasted over 120 min.

Table 1 Effects of TRH and TA-0910 on spontaneous motor activity and the number of falls in RMN (rol/rol)

Drug	*Dose*	n	*Spontaneous motor activity* (counts/10 min ± s.e.) *Pre*	*Post*	*No. of falls* (counts/10 min ± s.e.) *Pre*	*Post*
Saline	–	9	268.3 ± 39.0	205.8 ± 32.5	16.0 ± 2.4	16.1 ± 3.9
TRH	3	10	285.1 ± 35.1	407.0 ± 48.6	20.9 ± 3.1	22.1 ± 4.7
	30	9	221.4 ± 33.2	247.8 ± 56.3	15.8 ± 2.1	3.2 ± 0.5[a]
TA-0910	0.3	10	254.9 ± 29.6	427.2 ± 92.3	18.5 ± 7.2	22.9 ± 7.2
	3	10	244.7 ± 39.6	304.5 ± 73.0	17.3 ± 3.1	4.7 ± 2.3[a]

Pre-drug values were the means of 3 measurements made during 72–24 h before drug administration. Post-drug values of saline, TRH and TA-0910 were measured 10–20, 30–40 and 30–40 min after drug administration, respectively.

[a] P < 0.05 compared with the saline-treated control (Duncan's multiple range test).

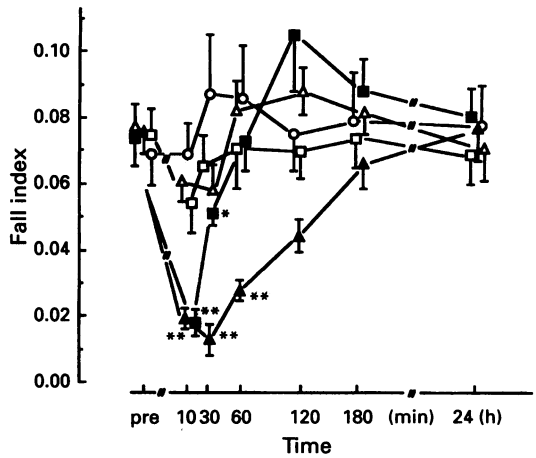


Figure 2 Effect of single intraperitoneal administration of TRH and TA-0910 on the fall index (number of falls/spontaneous motor activity for 10 min) in rolling mouse Nagoya (rol/rol) ($n=9-10$). Drugs were administered 10 min before placing the animal in the cage on a SCANETT for measurements. (○) Saline; (□) TRH 3 mg kg^{-1}; (■) TRH 30 mg kg^{-1}; (△) TA-0910 0.3 mg kg^{-1}; (▲) TA-0910 3 mg kg^{-1}. *$P<0.05$, **$P<0.01$ compared with control (ANOVA followed by Duncan's multiple range test).

The spontaneous motor activity did not change, even at the peak effect time for the fall index, i.e., 10 and 30 min after the administration of TRH and TA-0910, respectively. Rolling mice frequently fell with jerky movements of the hind limbs. Compared with the pre-treatment values in each group, the number of falls per 10 min markedly decreased after treatment with TRH at a dose of 30 mg kg^{-1} and with TA-0910 at a dose of 3 mg kg^{-1} ($F_{4,43}=5.921$, $P<0.05$; Duncan's multiple range test; Table 1). The decrease in the fall index in rolling mouse Nagoya indicated that TRH and TA-0910 depressed the occurrence of ataxia.

Autoradiographic study

The mean body weights of normal mice (RMN, +/+) treated with saline and rolling mice (RMN, rol/rol) treated with saline, TRH (30 mg kg^{-1}), and TA-0910 (3 mg kg^{-1}) were 35.6 g, 26.4 g, 25.9 g and 25.1 g, respectively. The mean body weight of the normal mice was significantly higher than those in the other three groups ($F_{3,28}=45.808$, $P<0.001$; multiple t test). After 2-DG injection, the animals showed exploratory behaviour for 1–2 min and then kept grooming. There were no differences in behaviour except the gait in RMN (rol/rol) among the 4 groups for the experimental period of 45 min.

Relative LCGU in the cerebellar cortex, cerebellar interposed nucleus, cerebellar lateral nucleus, ventral tegmental area (VTA) and the parietal cortex in the saline-treated rolling mice were lowered compared with the normal mice (23.9%, 21.1%, 22.5%, 14.2% and 16.3% decrease, respectively; $F_{3,28}=7.804$, $F_{3,28}=8.073$, $F_{3,28}=6.432$, $F_{3,27}=4.694$, $F_{3,28}=12.630$, respectively; $P<0.05$; multiple t test; Table 2). Although not statistically significant, LCGU in the thalamic nuclei tended to be lower in rolling mice than in normal mice. There were no significant differences in relative LCGU in other brain regions between RMN (+/+) and RMN (rol/rol).

TRH and TA-0910 increased relative LCGU in the VTA of rolling mice ($F_{3,27}=4.694$, $P<0.05$; multiple t test; Table 2). The LCGU in cerebellar cortex, cerebellar interposed nucleus and cerebellar lateral nucleus was the same between the drug-treated and the saline-treated rolling mice. In the TRH-treated rolling mice, relative LCGU also increased significantly in the caudate-putamen, medial septum, diagonal band of the vertical limb and thalamus (ventral, lateral and medial nucleus) (Table 2). On the contrary, TA-0910 significantly suppressed relative LCGU in the frontal and parietal cortices ($F_{3,28}=3.605$ and $F_{3,28}=12.630$, respectively; $P<0.05$; multiple t test; Table 2).

Discussion

TA-0910 has been developed as an anti-ataxic TRH analogue with minor hormonal activity. The depression of ataxia by TA-0910 was about 10 times as potent and more than twice as long-lasting as TRH when given intraperitoneally. Although the difference in the affinity for TRH-receptors has to be determined, this compound is metabolically more stable than TRH in the blood (Chishima, 1994) and brain (Kodama *et al.*, personal communication). The potent and long-lasting effect may be due to the better penetration to the brain and less degradation following administration.

The rolling mouse Nagoya (RMN, rol/rol) is an ataxic model with a histological alteration (Nishimura, 1975; Muramoto *et al.*, 1982) and altered neurotransmitter levels (Muramoto *et al.*, 1981) in the cerebellum. In the present study, relative LCGU was lower in the cerebellar structures, parietal cortex and VTA. Assuming that LCGU reflect local metabolic activities (Kennedy *et al.*, 1975; Sokoloff *et al.*, 1977; Yarowsky *et al.*, 1983), neuronal activities are depressed in these structures in rolling mice.

Among the structures with a low LCGU, the parietal cortex is not thought to be related to the control of motor functions. In TRH and TA-0910-treated rolling mice, the incidence of ataxia is depressed without a recovery in LCGU of the parietal cortex. Thus, the relationship between the ataxia and dysfunction of the parietal cortex is not clear. Likewise TRH and TA-0910 did not increase LCGU in the cerebellar cortex and nuclei. Rather, iontophoretically applied TRH decreased the firing rate of the cerebellar cortical neurones (Renaud *et al.*, 1975) and intravenously administered TRH decreased the LCGU in the cerebellar cortex in normal rats (Nagai *et al.*, 1980). Therefore, significant reduction of ataxia by TRH and TA-0910 is not due to amelioration of dysfunction in the cerebral cortex and the cerebellum in RMN.

VTA receives projections from the nucleus cuneiformis, the so-called mesencephalic locomotor region (Steeves & Jordan, 1984), and has functions as an operation system for muscle tonus (Mori *et al.*, 1982; 1989). A lower LCGU indicates that the function of the VTA is impaired in rolling mice. Electric lesions of the VTA induce several abnormal behaviours including hypereactivity (LeMoal *et al.*, 1976; Trovero *et al.*, 1992), postural tremor (Poirier, 1960) or tremor with rigidity (Pechadre *et al.*, 1976). In agreement with this, RMN often exhibited abnormal movement of the hind limbs. From these observations, ataxia in the rolling mice may result from dysfunction of the muscle tonus in the hind limbs due to dysfunction of the VTA. TRH and TA-0910 increased the depressed relative LCGU value in the VTA of rolling mice to the same level as in normal mice. Therefore, this finding strongly suggests that the amelioration of ataxia is due to activation of the VTA by TRH and TA-0910.

TRH increased the LCGU in the thalamus. TA-0910 also tended to increase the LCGU in the ventral and lateral nuclei of the thalamus. Although, the thalamus is a neural transit area among the cerebellar nuclei, basal ganglia and cerebral cortices, its role in motor function is still unclear in rodents. Although not statistically significant, LCGU in the rolling mouse tended to be lower than in normal mice. Therefore, the role of thalamic areas in the anti-ataxic effect of TA-0910 and TRH remains to be clarified.

There were some unexplained differences in LCGU between the TRH- and TA-0910-treated groups. For example, TA-0910 reduced LCGU in the cerebral cortices and TRH elevated it in some of the limbic structures while there were no parallel changes in the other drug-treated groups. These structures are among those in which LCGU was not significantly affected in the saline-treated ataxic RMN (except for the parietal cortex where LCGU was depressed). Therefore, the one-sided changes are probably unrelated to the anti-ataxic effects of these TRH agents.

It has been reported that the neuronal activity (Tomoda *et al.*, 1992), neurotransmitter concentration (Kato *et al.*, 1986)

Table 2 Effects of TRH and TA-0910 on relative local glucose utilization (LCGU) in Rolling mouse Nagoya (RMN)

Brain structures	*Relative LCGU*			
	RMN (+/+)	*RMN* (rol/rol)		
	Saline	*Saline*	*TRH* 30	*TA-0910* 3 (mg kg^{-1})
Cortex				
Frontal	2.44±0.09	2.45±0.09	2.69±0.20	2.11±0.09[b]
Parietal	2.63±0.13	2.20±0.08[a]	2.10±0.10	1.80±0.06[b]
Basal ganglia				
Caudate - putamen	2.66±0.06	2.76±0.14	3.38±0.14[b]	2.76±0.13
Globus pallidus	1.88±0.04	1.94±0.13	1.91±0.08	1.75±0.06
Entpeduncular n.	2.04±0.09	2.16±0.25	1.95±0.10	1.73±0.06
Subthalamic n.	2.98±0.23	2.65±0.18	2.59±0.10	2.33±0.11
Substantia nigra, comp.	2.43±0.12	2.11±0.09	2.33±0.11	2.29±0.15
Substantia nigra, ret.	1.98±0.09	1.73±0.08	1.87±0.14	1.61±0.07
Limbic structure				
Accumbens	2.08±0.07	2.12±0.09	2.06±0.10	1.96±0.11
Medial septum	2.29±0.11	2.22±0.12	2.65±0.12[b]	2.39±0.08
Diag. band, vertical limb	2.35±0.14	2.20±0.09	2.70±0.14[b]	2.42±0.14
Hippocampus, CA1	1.55±0.08	1.53±0.09	1.36±0.05	1.31±0.07
Hippocampus, CA2	1.44±0.20	1.57±0.09	1.44±0.20	1.57±0.09
Hippocampus, CA3	1.70±0.09	1.59±0.07	1.57±0.06	1.56±0.10
Hippocampus, dentate gyrus	1.73±0.09	1.57±0.10	1.60±0.05	1.50±0.09
Amygdala, centralis	1.29±0.07	1.22±0.09	1.05±0.05	1.12±0.06
Amygdala, lateralis	1.51±0.10	1.53±0.13	1.31±0.09	1.39±0.07
Thalamus				
Ventral n.	4.13±0.31	3.39±0.15	4.04±0.16[b]	3.58±0.25
Lateral n.	2.99±0.21	2.49±0.13	3.04±0.17[b]	2.59±0.14
Medial n.	3.75±0.27	3.06±0.15	3.64±0.17[b]	2.99±0.13
Hypothalamus				
Ventromedialis	1.25±0.07	1.15±0.03	1.10±0.07	1.15±0.05
Dorsomedialis	1.51±0.08	1.39±0.07	1.42±0.07	1.45±0.05
Lateralis	2.09±0.10	1.86±0.09	2.06±0.09	1.95±0.10
Cerebellum				
Cortex	2.68±0.18	2.04±0.11[a]	2.12±0.12	1.82±0.09
Interposed n.	2.66±0.18	2.10±0.08[a]	2.03±0.12	1.90±0.08
Lateral n.	2.80±0.24	2.17±0.07[a]	2.05±0.14	1.96±0.08
Brain stem				
Ventral tegmental area	2.33±0.11	2.00±0.08[a]	2.53±0.09[b]	2.33±0.11[b]
Inferior colliculus	3.55±0.21	3.11±0.15	3.21±0.32	2.77±0.17
Superior colliculus	2.12±0.14	1.97±0.16	2.00±0.17	1.77±0.08
Pedunculopontine tegmental n.	1.79±0.12	1.71±0.12	1.65±0.11	1.63±0.05
Red n.	2.54±0.17	2.44±0.17	2.78±0.15	2.54±0.13
Interpeduncular n.	2.80±0.16	2.57±0.12	2.71±0.12	2.56±0.13
White matter				
Corpus callosum	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00

Saline, TRH or TA-0910 was administered intraperitoneally to fasted normal (+/+) or ataxic (rol/rol) RMN immediately after ^{14}C-2DG injection. The animals were decapitated 45 min after the treatment. LCGU was measured as the grain density related to that of corpus callosum. The data are given as means±s.e.mean of 8 animals. See the text for more detail. [a] $P<0.05$ vs. saline-treated RMN (+/+) (multiple t test). [b] $P<0.05$ vs. saline-treated RMN (rol/rol) (multiple t test).

and LCGU (Kato *et al.*, 1982; Yamaguchi *et al.*, 1992) are altered in the basal ganglia of rolling mice. One may speculate that ataxia of rolling mice is induced by the abnormal function of the basal ganglia. However, there was no difference in LCGU in these structures between the rolling mice and normal mice. The reason for this discrepancy remains unclear. It may be worthwhile to consider that external conditions greatly influence the characters of animal strains (Stearns, 1989). The discrepancy may have derived from the difference in housing conditions of the animals. Therefore, it is premature to conclude whether the basal ganglia is involved in the ameliorating effect of the drugs.

In conclusion, TRH and TA-0910 clearly ameliorated the ataxia in the rolling mouse Nagoya. The LCGU values of the cerebellar cortex, cerebellar nuclei, parietal cortex and VTA in rolling mice were lower than those in normal mice, suggesting that ataxia in the rolling mice is mainly accompanied by an apparent reduced function of these brain structures. Since TRH and TA-0910 significantly increased the LCGU in the VTA, the anti-ataxic effect by TRH and TA-0910 in the rolling mice may be due to functional activation of the VTA region of the brain.

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References

BROWNSTEIN, M.J., PALKOVITS, M., SAAVEDRA, J.M., BASSIRI, R.M. & UTIGER, R.D. (1974). Thyrotropin-releasing hormone in specific nuclei of rat brain. *Science*, **185**, 267–269.

CHISHIMA, S. (1994). A radioimmunoassay for TA-0910, a new metabolically stable thyrotropin-releasing hormone analogue, *J. Pharm. Biomed. Anal.*, **12**, 795–804.

HASHIMOTO, T & FUKUDA, N. (1990). Effect of thyrotropin-releasing hormone on the time course of neurologic recovery after spinal cord injury in the rat. *Jpn. J. Pharmacol.*, **53**, 479–486.

KARDON, F.C., WINOKUR, A. & UTIGER, R.D. (1977). Thyrotropin-releasing hormone (TRH) in rat spinal cord. *Brain Res.*, **122,** 578–581.

KATO, M., HOSOKAWA, S., TOBIMATSU, S. & KUROIWA, Y. (1982). Increased local cerebral glucose utilization in the basal ganglia of the Rolling mouse Nagoya. *J. Cereb. Blood Metabol.*, **2,** 385–393.

KATO, M., YOSHIDA, M. & ARIGA, T. (1986). GABA and glutamic acid concentrations in the globus pallidus and substantia nigra of the Rolling mouse Nagoya. *Neurosci. Res. Suppl.* **3,** S81.

KENNEDY, C., DES ROSIERS, M.H., JEHLE, J.W., REIVICH, M., SHARPE, F. & SOKOLOFF, L. (1975). Mapping of functional neural pathways by autoradiographic survey of local metabolic rate with [^{14}C] deoxyglucose. *Science*, **187,** 850–853.

KINOSHITA, K., FUJITSUKA, T., YAMAMURA, M. & MATSUOKA, Y. (1995). Effects of TA-0910, a novel orally active thyrotropin-releasing hormone analog, on the gait of ataxic animal models. *Eur. J. Pharmacol.*, **274,** 65–72.

KURIHARA, E., FUKUDA, N., NARUMI, S., MATSUO, T., SAJI, S. & NAGAWA, Y. (1985). Effects of thyrotropin-releasing hormone tartrate (TRH-T) and its main metabolite Histidyl-Proline Diketopiperazine on the walking ataxia in Rolling mouse Nagoya. *Jpn. Pharmacol. Ther.*, **13,** 49–56 (in Japanese).

LEMOAL, M., STINUS, L. & GALEY, D. (1976). Radio-frequency lesions of the ventral mesencephalic tegmentum: neurological and behavioral considerations. *Expl. Neurol.*, **50** 521–535.

MANO, Y., MATSUI, K., TOYOSHIMA, E. & ANDO, K. (1986). The pharmacological effect of thyrotropin-releasing hormone on ataxic mutant mice. *Acta. Neurol. Scand.*, **73,** 352–358.

MORI, S., KAWAHARA, K., SAKAMOTO, T., AOKI, M. & TOMIYAMA, T. (1982). Setting and resetting of postural muscle tone in the decerebrate cat by stimulation of the brain stem. *J. Neurophysiol.*, **48,** 737–748.

MORI, S., SAKAMOTO, T., OHTA, Y., TAKAKUSAKI, K. & MATSUYAMA, K. (1989). Site-specific postural and locomotor change evoked in awake, freely moving intact cats by stimulating the brain stem. *Brain Res.*, **505,** 66–74.

MURAMOTO, O., ANDO, K. & KANAZAWA, I. (1982). Central noradrenaline metabolism in cerebellar ataxic mice. *Brain Res.*, **237,** 387–395.

MURAMOTO, O., KANAZAWA, I. & ANDO, K. (1981). Neurotransmitter abnormality in Rolling mouse Nagoya, an ataxic mutant mouse. *Brain Res.*, **215,** 295–304.

NAGAI, Y., NARUMI, S., NAGAWA, Y., SAKURADA, O., UENO, F. & ISHII, S. (1980). Effect of thyrotropin-releasing hormone (TRH) on local cerebral glucose utilization, by the autoradiographic 2-deoxy [^{14}C] glucose method, in conscious and pentobarbitalized rats. *J. Neurochem.*, **35,** 963–971.

NISHIMURA, Y. (1975). The cerebellum of rolling mouse Nagoya. *Adv. Neurol. Sci.*, **19,** 670–672 (in Japanese).

OLIVER, C., ESKAY, R.L., BEN-JONATHAN, N. & PORTER, J.C. (1974). Distribution and concentration of TRH in the rat brain. *Endocrinology*, **95,** 540–546.

PECHADRE, J.C., LAROCHELLE, L. & POIRIER, L.J. (1976). Parkinsonian akinesia, rigidity and tremor in the monkey. *J. Neurol. Sci.*, **28,** 147–157.

POIRIER, L.J. (1960). Experimental and histological study of midbrain dyskinesias. *J. Neurophysiol.*, **23,** 534–551.

RENAUD, L.P., MARTIN, J.B. & BRAZEAU, P. (1975). Depressant action of TRH, LH-RH and somatostatin on activity of central neurons. *Nature*, **255,** 233–235.

SHARP, F.R., KILDUFF, T.S., BZORGCHAMI, S., HELLAR, H.C. & RYAN, A.F. (1983). The relationship of local cerebral glucose utilization to optical density ratios. *Brain Res.*, **263,** 97–103.

SHARP, T., BENNETT, G.W., MARSDEN, C.A. & TULLOCH, I.F. (1984a). A comparison of the locomotor effects induced by centrally injected TRH and TRH analogues. *Regul. Pept.*, **9,** 305–315.

SHARP, T., TULLOCH, I.F., BENNETT, G.W., MARSDEN, C.A., METCALF, G. & DETTMAR, P.W. (1984b). Analeptic effects of centrally injected TRH and analogues of TRH in the pentobarbitone-anaesthetized rat. *Neuropharmacology*, **23,** 339–348.

SOKOLOFF, L., REIVICH, M., KENNEDY, C., DES ROSIERS, M.H., PATLAK, C.S., PETTIGREW, K.D., SAKURADA, O. & SHINOHARA, M. (1977). The [^{14}C] deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure, and normal values in the conscious and anesthetized albino rat. *J. Neurochem.*, **28,** 897–916.

STEARNS, S.C. (1989). The evolutionary significance of phenotypic plasticity. *BioScience*, **39,** 436–445.

STEEVES, J.D. & JORDAN, L.M. (1984). Autoradiographic demonstration of the projections from the mesencephalic locomotor region. *Brain Res.*, **307,** 263–276.

TOMODA, H., KATO, M., SAKATA, S. & SHIMA, F. (1992). Striatal dysfunction in Rolling mouse Nagoya: an electrophysiological study. *J. Neurol. Sci.*, **112,** 106–112.

TROVERO, F., BLANC, G., HERVÊ, D., VÊZINA, P., GLOWINSKI, J. & TASSIN, J.-P. (1992). Contribution of an α_1-adrenergic receptor subtype to the expression of the 'ventral tegmental area syndrome'. *Neurosci.*, **47,** 69–76.

YAMAGUCHI. T., KATO, M., FUKUI, M. & AKAZAWA, K. (1992). Rolling dysfunction: determination of absolute rates of local cerebral glucose utilization. *Brain Res.*, **298,** 38–44.

YAMAMOTO, M. & SHIMIZU, M. (1989). Effect of YM-14673, a new thyrotropin-releasing hormone analogue, on ataxic gait in cytosine arabinoside-treated mice. *Eur. J. Pharmacol.*, **166,** 545–547.

YAROWSKY, P., KADEKARO, M. & SOKOLOFF, L. (1983). Frequency-dependent activation of glucose utilization in the superior cervical ganglion by electrical stimulation of cervical sympathetic trunk. *Proc. Natl. Acad. Sci. U.S.A.*, **80,** 4179–4183.

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