Alterations in Local Cerebral Glucose Metabolism and Endogenous Thyrotropin-Releasing Hormone Levels in Rolling Mouse Nagoya and Effect of Thyrotropin-Releasing Hormone Tartrate

Takahiro Nakayama and Yasuo Nagai

Pharmaceutical Research Laboratories I, Pharmaceutical Research Division, Takeda Chemical Industries, Ltd.,
17-85 Juso-honmachi 2-chome, Yodogawa-ku, Osaka 532, Japan

Received July 4, 1996 Accepted August 20, 1996

ABSTRACT—To identify the brain region(s) responsible for the expression of ataxic gaits in an ataxic mutant mouse model, Rolling mouse Nagoya (RMN), changes in local cerebral glucose metabolism in various brain regions and the effect of thyrotropin-releasing hormone tartrate (TRH-T), together with alterations in endogenous thyrotropin-releasing hormone (TRH) levels in the brains of RMN, were investigated. Ataxic mice [RMN (rol/rol)] showed significant decreases in glucose metabolism in regions of the diencephalon: thalamic dorsomedial nucleus, lateral geniculate body and superior colliculus; brain stem: substantia nigra, raphe nucleus and vestibular nucleus; and cerebellar nucleus as compared with normal controls [RMN (+/+)]. When RMN (rol/rol) was treated with TRH-T (10 mg/kg, equivalent to 7 mg/kg free TRH), glucose metabolism was significantly increased in these regions. These results suggest that these regions may be responsible for ataxia. We also found that TRH levels in the cerebellum and brain stem of RMN (rol/rol) were significantly higher than those of RMN (+/+). These results suggest that ataxic symptoms in RMN (rol/rol) may relate to the abnormal metabolism of TRH and energy metabolism in the cerebellum and/or brain stem and that exogenously given TRH normalizes them.

Keywords: Thyrotropin-releasing hormone tartrate, Local cerebral glucose metabolism, Rolling mouse Nagoya

Thyrotropin-releasing hormone (TRH) is a hypo-thalamic tripeptide (L-pyroglutamyl-L-histidyl-L-proline amide) neurohormone that stimulates the release and synthesis of thyrotropin from the anterior pituitary via the hypophyseal portal system. In addition, TRH is known to have profound pharmacological effects on the central nervous system that are independent of the hypothalamic-pituitary-thyroid axis [e.g., modulation of the monoaminergic system, enhancement of learning and memory functions, and antagonism of hypnotic, sedative and hypothermic states (1–6), etc.].

Rolling mouse Nagoya (RMN), an animal model of hereditary cerebellar ataxia, is a neurological mutant mouse that shows marked motor disturbances in the hind limbs, such as frequent lurching and falling over when walking. In previous biochemical studies, it has been found to exhibit abnormalities of noradrenaline (7, 8), glutamate, glycine and taurine (9) in the cerebellum, although anatomical studies revealed no gross anatomical

derangements in this region (8–12). The rate of local cerebral glucose utilization (LCGU) has been shown to correlate closely with local functional activity (13). However, it is difficult to measure an absolute rate of LCGU in mice because of insufficient collection of several timed arterial blood samples. We measured regional glucose uptake into the brain of RMN in vivo instead of LCGU. Some of the changes in glucose metabolism observed in the RMN have been thought to be due to functional deficiency and pathological changes. Therefore, glucose uptake could be useful for identifying the brain region(s) responsible for the expression of ataxic gaits and the effects of drugs on these areas. Sobue et al. reported that TRH was involved in the amelioration of ataxia of spinocerebellar degenerative disease (14, 15). Also, Kurihara et al. reported that in RMN, exogenously administered TRH tartrate (TRH-T) and its main metabolite histidyl-proline diketopiperazine ameliorated the ataxic gait (16). They obtained data showing that
TRH-T had a significant effect on the ataxic symptom at doses of 10 and 25 mg/kg (7 and 17 mg/kg as free TRH) but not at 4 mg/kg (2.8 mg/kg as free TRH). In the present study, we measured glucose uptake into various brain regions of RMN and the effect of TRH-T on them at a dose of 10 mg/kg, as well as alterations in endogenous TRH levels, in order to identify the brain region(s) responsible for the expression of ataxic gait in RMN.

MATERIALS AND METHODS

Animals

Male Rolling mouse Nagoya (RMN, strain: C3H-HE), +/+ (normal controls without ataxic gaits, 12- to 14-weeks-old) and rol/rol (genotype exhibiting ataxic gaits, 12- to 14-weeks-old), obtained from the Takatsuki Drug Safety Laboratories at Takeda Chemical Ind., Ltd., were used in these experiments. The animals were maintained under controlled environmental conditions (12-hr dark/light cycle, 24 ± 1°C and 55 ± 5% relative humidity) and given free access to a standard diet and water.

Chemicals

TRH-T (thyrotropin-releasing hormone tartrate, Lot No. OB021) was synthesized in our laboratories and was used after being dissolved in saline (10 mg/2 ml saline). 2-Deoxy-[14C]-D-glucose (specific radioactivity: 1.85-2.22 Gbq/mmol) was purchased from American Radiolabeled Chemicals (St. Louis, MO, USA). Glucose oxidase (grade II), peroxidase (grade II) and ABTS® (2,2'-azino-di-[3-ethyl-benzthiazolinsulfonat<6>) were purchased from Boehringer-Mannheim Yamanouchi (Tokyo). Glucose standard solution (300 mg/dl) was obtained from Wako Pure Chemical Ind. (Osaka), All other chemicals were of analytical reagent grade.

Determination of regional glucose uptake

Animals (RMN, 12- to 14-weeks-old) were deprived of food for approximately 17 hr prior to the experiment to stabilize plasma glucose levels. Animals were given TRH-T (10 mg/kg, equivalent to 7 mg/kg free TRH) or saline subcutaneously; then 20 min later, [14C]deoxy-D-glucose (100 μCi/kg/10 ml) was injected intraperitoneally. The animals were sacrificed by decapitation 30 min after injection of the radiotracer. Blood was sampled and immediately centrifuged, and plasma samples were analyzed for 14C by liquid scintillation spectroscopy and for plasma glucose by the glucose oxidase method (17). The brain was dissected, coated with chilled embedding medium (Lipshaw Manufacturing Co., Detroit, MI, USA) and frozen in isopentane with dry ice. Once fully frozen, the brain was stored at −70°C prior to sectioning. Frozen coronal sections (20 μm) were obtained using a cryostat (−22°C), mounted onto glass coverslips and rapidly dried on a hotplate (60°C). Sections were exposed to SB X-ray film (Kodak, Tokyo) for 10 days, together with a set of [14C] plastic standards. Images were processed using a photo film developer and fixer (Fuji Film, Osaka). Autoradiograms were analyzed for local cerebral glucose metabolism using a quantitative imaging system (Micro Computer Imaging Device; Imaging Research, St. Catharines, Ontario, Canada).

The glucose uptake into various brain regions was calculated by the following equation:

\[
\text{Regional glucose uptake (mg/g tissue)} = \frac{\text{regional [14C] density (DPM/g tissue)} \times \text{plasma glucose level (mg/ml)} \times \text{plasma [14C]deoxy-D-glucose level (DPM/ml)}}{\text{plasma [14C]deoxy-D-glucose level (DPM/ml)}}
\]

The stereotaxic atlas of the rat brain compiled by Pellegrino and Cushman (18) was used to define the different brain areas.

Determination of endogenous TRH levels in the brains of RMN

Animals (RMN, 12- to 14-weeks-old) were sacrificed by focused microwave irradiation (8 kW, 0.85 sec), and then the brain tissues were dissected and divided into 5 parts (cerebellum, brain stem, diencephalon, cerebral cortex and hippocampus). The specimens were quickly weighed, homogenized with 10 ml cold methanol and centrifuged (8,000 x g, 10 min). The resultant supernatants were dried under N2 gas. Petroleum ether was added to the residues to remove lipid and was then aspirated. The residues were then suspended in water and centrifuged to remove excess proteins. Extracted endogenous TRH concentrations in each part of the brain were measured by radioimmunoassay and expressed as ng/g of wet weight. TRH recovery rate from the brain was determined in a preliminary study in which various concentrations of authentic TRH were added to the brain tissues.

These experiments were conducted in accordance with The Takeda Experimental Animal Care and Use Committee.

Statistical analyses

Differences of glucose uptake between the RMN (+/+) group and the saline-treated RMN (rol/rol) group and of TRH levels between them were evaluated by Student's t-test. Differences of glucose uptake between the saline-treated and TRH-T-treated RMN (rol/rol) group were evaluated, only in each brain region where there was a significant change in the saline-treated RMN (rol/rol) as compared with RMN (+/+) , by Student's t-test. Statistical significance was taken to be P < 0.05.
RESULTS

Changes in glucose uptake in various brain regions and effects of TRH-T

As shown in Table 1, mean values for glucose uptake in the 35 brain regions studied in RMN (+/+) and saline-treated RMN (rol/rol) were 6.61 ± 0.30 mg/g tissue and 5.68 ± 0.22 mg/g tissue, respectively, indicating that the overall glucose uptake in RMN (rol/rol) was 85.9% of that in RMN (+/+) (data not shown). Glucose uptake

| Structure                        | RMN (+/+) (n=6) | Saline (n=6) | TRH-T (10 mg/kg) (n=7) |
|----------------------------------|-----------------|--------------|------------------------|
| Visual cortex                    | 5.19 ± 0.29     | 4.59 ± 0.24  | 5.08 ± 0.49            |
| Auditory cortex                  | 4.84 ± 0.40     | 3.95 ± 0.27  | 4.76 ± 0.28            |
| Parietal cortex                  | 6.56 ± 0.49     | 5.65 ± 0.35  | 7.16 ± 0.55            |
| Sensory-motor cortex             | 5.78 ± 0.53     | 5.54 ± 0.38  | 7.34 ± 0.53            |
| Olfactory cortex                 | 5.86 ± 0.47     | 5.35 ± 0.25  | 5.85 ± 0.36            |
| Frontal cortex                   | 4.88 ± 0.49     | 4.91 ± 0.31  | 6.16 ± 0.38            |
| Thalamus: Lateral nucleus        | 7.87 ± 0.71     | 6.87 ± 0.38  | 9.26 ± 0.63            |
| Ventral nucleus                  | 7.09 ± 0.55     | 6.65 ± 0.53  | 9.16 ± 0.57            |
| Dorsomedial nucleus              | 9.01 ± 0.51     | 7.45 ± 0.43  | 10.38 ± 0.89*          |
| Habenula                         | 8.64 ± 0.58     | 7.64 ± 0.39  | 10.54 ± 0.84           |
| Subthalamus nucleus              | 7.14 ± 0.53     | 6.63 ± 0.45  | 9.09 ± 0.65            |
| Medial geniculate body           | 6.30 ± 0.44     | 6.17 ± 0.33  | 7.76 ± 0.43            |
| Lateral geniculate body          | 8.14 ± 0.49     | 6.41 ± 0.41  | 9.63 ± 0.80#           |
| Hypothalamus                     | 3.94 ± 0.41     | 3.49 ± 0.26  | 4.57 ± 0.28            |
| Mamillary body                   | 10.60 ± 0.94    | 8.23 ± 0.39  | 9.83 ± 0.69            |
| Hippocampus: Ammon’s horn        | 6.16 ± 0.47     | 5.50 ± 0.35  | 7.20 ± 0.56            |
| Dentate gyrus                    | 4.22 ± 0.45     | 3.38 ± 0.31  | 4.40 ± 0.31            |
| Amygdala                         | 4.02 ± 0.49     | 3.26 ± 0.31  | 4.55 ± 0.31            |
| Septal nucleus                   | 6.01 ± 0.52     | 5.61 ± 0.48  | 7.83 ± 0.55            |
| Caudate-putamen                  | 7.19 ± 0.48     | 7.14 ± 0.44  | 10.19 ± 0.73           |
| Nucleus accumbens                | 5.01 ± 0.47     | 4.40 ± 0.46  | 6.60 ± 0.38            |
| Globus pallidus                  | 4.33 ± 0.33     | 5.18 ± 0.25  | 6.64 ± 0.32            |
| Substantia nigra                 | 6.36 ± 0.58     | 4.82 ± 0.24  | 6.55 ± 0.37#           |
| Raphe nucleus                    | 8.85 ± 0.76     | 6.18 ± 0.37  | 8.81 ± 0.53#           |
| Locus cereuleus                  | 7.46 ± 0.66     | 6.36 ± 0.31  | 8.31 ± 0.61            |
| Vestibular nucleus               | 9.30 ± 0.66     | 6.91 ± 0.41  | 9.39 ± 0.58#           |
| Cochlear nucleus                 | 7.22 ± 0.51     | 6.39 ± 0.31  | 7.83 ± 0.66            |
| Superior olivary nucleus         | 7.50 ± 0.61     | 6.74 ± 0.28  | 7.83 ± 0.53            |
| Lateral lemniscus                | 6.14 ± 0.50     | 5.48 ± 0.39  | 6.86 ± 0.37            |
| Inferior colliculus              | 9.70 ± 0.88     | 7.57 ± 0.39  | 9.00 ± 0.50            |
| Superior colliculus              | 7.30 ± 0.67     | 5.12 ± 0.41  | 6.70 ± 0.43#           |
| Pontine gray matter              | 5.41 ± 0.60     | 4.98 ± 0.45  | 6.95 ± 0.56            |
| Cerebellar cortex                | 5.65 ± 0.43     | 4.55 ± 0.28  | 6.27 ± 0.61            |
| Cerebellar nucleus               | 7.83 ± 0.60     | 6.22 ± 0.39  | 8.49 ± 0.60#           |
| Internal capsule                 | 3.72 ± 0.34     | 3.48 ± 0.35  | 4.72 ± 0.35            |

TRH-T (10 mg/kg, equivalent to 7 mg/kg free TRH) or saline was administered subcutaneously 20 min before intraperitoneal injection of 2-deoxy-[14C]-D-glucose. Mice were sacrificed by decapitation 30 min after injection of the radiotracer, and glucose uptake into each brain region was calculated from the regional 14C density in the autoradiogram, plasma glucose level and 14C level. Each value represents the mean ± S.E. for 6–7 animals. *P<0.05, compared with the RMN (+/+) group; #P<0.05, ##P<0.01 compared with the saline-treated RMN (rol/rol) (Student’s t-test).
was significantly decreased in 7 out of the 35 regions (thalamic dorsomedial nucleus, lateral geniculate body, substantia nigra, raphe nucleus, vestibular nucleus, superior colliculus and cerebellar nucleus). When the glucose uptake in RMN (rol/rol) treated with TRH-T (10 mg/kg, equivalent to 7 mg/kg free TRH) was determined 20 min after treatment, the glucose uptakes in the 7 above-mentioned areas were significantly recovered.

Fig. 1. Recovery of TRH from the brain tissue of Rolling mouse Nagoya. TRH concentration was measured by radioimmunoassay after extraction.

Changes in endogenous TRH levels in the brains of RMN

The recovery rate for the methanol extraction of authentic TRH from brain tissue is shown in Fig. 1. The rate was calculated to be 84.2% (range 0–200 ng/g tissue) of the added TRH concentration. As shown in Fig. 2, TRH concentrations in the brains of RMN (rol/rol) were significantly higher in the cerebellum and brain stem than those in the controls [(RMN (+/+)] (+41% and +56%, respectively), while concentrations in the cerebral cortex and hippocampus were not significantly different from those in the controls. TRH concentrations in the diencephalon in RMN (rol/rol) showed a tendency to increase in comparison with the control (+54%).

DISCUSSION

It has been reported that treatment with TRH ameliorates ataxia in spinocerebellar disease and mice with hereditary ataxia (14, 15), but the mechanism by which TRH lessens ataxic symptoms remains unclear. We reasoned that measurement of local cerebral glucose metabolism and TRH concentrations in the brain of the ataxic mouse would serve to disclose the mechanism underlying its ataxia-reducing effect and the pathophysiological significance of TRH in this mouse model. The present study showed that glucose metabolism in the brain of RMN (rol/rol) was significantly decreased in regions of the diencephalon: thalamic dorsomedial nucleus, lateral geniculate body and superior colliculus; brain stem: substantia nigra, raphe nucleus and vestibular nucleus; and cerebellar nucleus, indicating that these regions may be responsible for the expression of ataxic gaits. Treatment with TRH-T (10 mg/kg, equivalent to 7 mg/kg free TRH, s.c.) significantly reversed the decrease in these regions, suggesting that TRH-T can ameliorate motor disturbances by normalizing defective glucose metabolism in the cerebellum, brain stem and diencephalon. Yamaguchi et al. reported that RMN (rol/rol) showed marked increases in LCGU in areas of the basal ganglia such as the globus pallidus, entopeduncular nucleus, substantia nigra pars compacta and pars reticulata, and subthalamic nucleus (19), indicating that dysfunction in the basal ganglia is the major cause of the motor disturbance observed in RMN (rol/rol). On the other hand, Kinoshita et al. recently demonstrated, using relative LCGU values in various regions of the white matter, that RMN (rol/rol) show significant decreases in the cerebellum, parietal cortex and ventral tegmental area (VTA) compared with controls and that intraperitoneal
injection of TRH or its analogue TA-0910 reverses the decrease in relative LCGU in the VTA but not in the cerebellum or parietal cortex (20). This suggests that the effect of TRH on ataxia in RMN (rol/rol) might result from functional activation of the VTA. The present results coincide with those of Yamaguchi et al. in that a moderate increase in glucose metabolism was observed in the globus pallidus in the brain of RMN (rol/rol), but do not thoroughly reproduce the finding that glucose metabolism in each brain region of RMN (rol/rol) was higher than that in the controls. The results of Kinoshita et al. mostly coincide with our present results from the point of view of showing an extensive decrease in each brain region of RMN (rol/rol) with that in the controls. The results of Kinoshita et al. mostly coincide with our present results from the point of view of showing an extensive decrease in each brain region of RMN (rol/rol), including the cerebellar areas. However, there was a minor discrepancy, the reason for which remains unclear. It may have originated from differences in the housing conditions of the animals, strain, gender and/or age used in each experiment. Further investigation will be necessary to obtain a definite conclusion.

The present study demonstrated that the TRH concentrations in the brains of RMN (rol/rol) were higher in the cerebellum, brain stem and diencephalon than those in the controls. These results suggest that abnormalities of the utilization of TRH may exist in these regions in RMN (rol/rol). Endo et al. reported that serotonergic agonists suppressed TRH release in the spinal cord of the RMN via autoreceptors, leading to an increased TRH content. This suggested that in the RMN, the dysfunction in the serotonergic nerve system may be attributable to the TRH turnover (21). There are also a number of reports of a positive correlation between serotonergic hyperactivity and motor disturbance. Ikeda et al. demonstrated the involvement of serotonergic neuronal hyperactivity (e.g., enhanced serotonin synthesis) in the manifestation of involuntary movements in another mutant mouse, Wringle Mouse Sagami (WMS) (22). It is conceivable that TRH release may be inhibited as a result of serotonergic hyperactivity in the cerebellum, brain stem and diencephalon. The present results regarding TRH contents in the RMN coincide with those of a previous study by Mitsuma et al. (23). They studied TRH levels in the brain of the Weaver ataxic mouse, the Purkinje cell degenerative ataxic mouse (pcd-ataxic mouse) and the cytosine arabinoside (ara-C)-induced ataxic mouse and demonstrated that TRH levels were significantly higher in the cerebellum and brain stem in the brains of Weaver and ara-C-induced ataxic mice and in the brain stem and cerebrum in the pcd-ataxic mouse. Thus, it was suggested that abnormalities in turnover of TRH (e.g., synthesis, release and metabolism) might exist in these brain regions of various ataxic animals including the RMN expressing ataxic gaits. Exogenously given TRH may normalize the serotonergic hyperactivity in the cerebellum, brain stem

---

**Fig. 2.** Concentrations of immunoreactive TRH in various brain regions of Rolling mouse Nagoya. Each animal was sacrificed by focused microwave irradiation (8 kW, 0.85 sec), and the brain tissues were dissected out and divided into five portions. TRH levels were measured by radioimmunoassay. The open columns and stippled columns represent the RMN (+/+) (n=6) and RMN (rol/rol) (n=5) group, respectively. Data are expressed as means±S.E. (vertical bars). *P<0.05, **P<0.01, compared with RMN (+/+)(Student's t-test).
and diencephalon by a feedback control and recover an endogenous TRH release in these regions. Consequently, it may ameliorate ataxic gaits of RMN.

In conclusion, we found that glucose uptakes in the cerebellum (cerebellar nucleus), brain stem (substantia nigra, raphe nucleus and vestibular nucleus) and diencephalon (thalamic dorsomedial nucleus, lateral geniculate body and superior colliculus) in RMN (rol/rol) were decreased, while TRH concentrations in the brains of RMN (rol/rol) were significantly higher in the cerebellum and brain stem than in the controls, suggesting that the ataxic symptoms in RMN (rol/rol) might result primarily from a functional abnormality in the cerebellum and/or brain stem and that exogenously administered TRH normalized the functional abnormality in these regions.

REFERENCES

1. Burgus R, Dunn TE and Desiderio T: Characterization of ovine hypothalamic hypophysiotrophic TSH-releasing factor. Nature 226, 321–325 (1970)
2. Lechan RM, Wu P and Jackson IMD: Immunolocalization of the thyrotropin-releasing hormone/prohormone in the rat central nervous system. Endocrinology 119, 1210–1216 (1986)
3. Sharif NA: Diverse role of thyrotropin-releasing hormone in brain, pituitary and spinal function. Trends Pharmacol Sci 6, 119–122 (1985)
4. Giovannini MG, Casamenti F, Nstri A, Paoli F and Pepeu G: Effect of thyrotropin-releasing hormone (TRH) on acetylcholine release from different brain areas investigated by microdialysis. Br J Pharmacol 102, 363–368 (1991)
5. Okada M: Effects of a new thyrotropin-releasing hormone analogue, YM-14673, on the release in vivo of acetylcholine as measured by intracerebral dialysis in rats. J Neurochem 56, 1544–1547 (1991)
6. Toide K, Shinosa M, Takase M, Iwata K and Yoshida H: Effects of a novel thyrotropin-releasing hormone analogue, JTP-2942, on extracellular acetylcholine and choline levels in the rat frontal cortex and hippocampus. Eur J Pharmacol 233, 21–28 (1993)
7. Adachi K, Sobue I, Tohyama M and Shinizu N: Changes in the cerebellar noradrenaline nerve terminals of the neurological murine mutant Rolling mouse Nagoya: a histofluorescence analysis. IRCS Med Sci 3, 329–330 (1975)
8. Konagaya M, Takayanagi T, Muroga T, Adachi K and Sobue I: Noradrenaline metabolism in the brain of Rolling mouse Nagoya and the influence of thyrotropin releasing hormone. Clin Neurol 20, 181–188 (1980)
9. Muramoto O, Kanazawa I and Ando K: Neurotransmitter abnormality in Rolling mouse Nagoya, an ataxic mutant mouse. Brain Res 215, 295–304 (1981)
10. Mukoyama M and Mizuno K: The cerebellum of Rolling mouse Nagoya. Light- and electronmicroscopic observation. Saishin-Igaku 31, 233–236 (1976) (in Japanese)
11. Nishimura Y: The cerebellum of Rolling mouse Nagoya. Adv Neurol Sci 19, 670–672 (1975)
12. Nishimura Y: Rolling mouse Nagoya; b. Study on the cells of cerebellar cortex and the clinical feature. Saishin-Igaku 31, 226–232 (1976) (in Japanese)
13. Sokoloff L: Relationship between physiological function and energy metabolism in the central nervous system. J Neurochem 29, 13–26 (1977)
14. Sobue I, Yamamoto H, Konagaya M, Iida M and Takayanagi T: Effect of thyrotropin-releasing hormone on ataxia of spinocerebellar degenerations. Lancet 1, 418–419 (1980)
15. Sobue I, Takayanagi T, Nakanishi T, Tsukubaki T, Ueno M, Kinoshita M, Igata A, Miyazaki M, Yoshida M, Ando K, Maruyama S, Mitsuma T, Nikiel N, Sakuma A and Kato K: Controlled trial of thyrotropin releasing hormone tartrate in ataxia of spinocerebellar degenerations. J Neurol Sci 61, 235–248 (1983)
16. Kurihara E, Fukuda N, Narumi S, Matsuo T, Saji S and Nagawa Y: 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 (1985) (in Japanese)
17. Werner W, Rey HG and Wielinger H: Uber die Eigenschaften eines neuen Chromagens fur Blutzuckerbestimmung nach der GOD/POD-Methode. Z Anal Chem 252, 224–228 (1970) (Abstr in English)
18. Pellegrino LJ and Cushman AJ: Stereotaxic Atlas of the Rat Brain. Appleton-Century-Crofts, New York (1967)
19. Yamaguchi T, Kato M, Fujii M and Akazawa K: Rolling mouse Nagoya as a mutant animal model of basal ganglia dysfunction: determination of absolute rates of local cerebral glucose utilization. Brain Res 598, 38–44 (1992)
20. Kinoshita K, Watanabe Y, Asai H, Yamamura M and Matsuoka Y: Anti-ataxic effects of TRH and its analogue, TA-0910, in Rolling mouse Nagoya by metabolic normalization of the ventral tegmental area. Br J Pharmacol 116, 3274–3278 (1995)
21. Endo S, Itoh M and Serizawa O: Serotonergic regulation of the spinal cord content of thyrotropin releasing hormone in the cerebellar ataxia mutant mouse. J Neurol Sci 118, 194–201 (1993)
22. Ikeda M, Mikuni M, Nishikawa T and Takahashi K: A neurochemical study of a new mutant mouse presenting myoclonus-like involuntary movement: a possible model of spontaneous serotonergic hyperactivity. Brain Res 495, 337–348 (1989)
23. Mitsuma T, Adachi K and Ando K: Concentration of thyrotropin-releasing hormone in the brain of ataxic mice. J Neurol Sci 75, 135–139 (1986)