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Effects of RGH-2202 on Behavioral Deficits After Focal Cerebral Ischemia in Rats

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NODA, Y., K. FURUKAWA, H. KOHAYAKAWA AND M. OKA. *Effects of RGH-2202 on behavioral deficits after focal cerebral ischemia in rats.* PHARMACOL BIOCHEM BEHAV **52**(4) 695-699, 1995.—We investigated the effects of RGH-2202 {posatirelin, (−)-(2S)-*N*-[(1S)-1-[[(2S)-2-carbamoyl-1-pyrrolidinyl[carbonyl]-3-methylbutyl]-6-oxopipecolamide}, a thyrotropin-releasing hormone (TRH) analog, on behavioral changes during a chronic phase of focal ischemia in rats in comparison with the parent peptide. The left middle cerebral artery (MCA) was occluded under halothane anesthesia, and the subsequent behavioral changes were observed for 35 days. RGH-2202 (1, 3, and 10 mg/kg) and TRH (10 mg/kg) were given IP just after the operation and afterward once a day for 14 days. MCA-occluded rats exhibited neurologic symptoms including hemiplegia and abnormal posture and disturbance of passive avoidance learning during the entire 35-day observation period. The repeated treatment with either peptides improved the neurologic and cognitive deficits. In addition, a recovery from deficits was still advanced after discontinuation of the drug treatment. In these effects, RGH-2202 was about three times more potent than TRH. Neural tissue damage in drug-treated groups, measured by ω_3 binding site densities 35 days after MCA occlusion, was inclined to be less than that in the vehicle-treated group. These results suggest that appropriate treatment with RGH-2202 may be useful in the treatment of functional disturbances after focal cerebral ischemia.

RGH-2202 Posatirelin TRH Focal cerebral ischemia Middle cerebral artery Hemiplegia Abnormal posture Cognitive deficit ω_3 binding sites

STROKE is a life-threatening event that often relapses and results in death or severe neurologic and cognitive deficits. Several drugs acting on cerebral circulation and metabolism have been used in the treatment of stroke (4,12,16). These drugs are proved to alleviate subjective symptoms such as dizziness and headache and to cause mood elevation, but are generally weak in improving neurologic and cognitive symptoms.

Thyrotropin-releasing hormone (TRH) has been considered to be of potential benefit in the treatment of stroke (6,9). Some of its stabilized analogs were shown to reduce biochemical and functional changes in some animal models of ischemic stroke (10,15,18,19,21,22). Shrewsbury-Gee et al. (18) reported that the acute intracerebroventricular injection of RX77368 protected the loss of somatosensory-evoked potential and reduced the area of infarct following middle cerebral artery (MCA) occlusion in rats. Yamamoto et al. (21) also showed ameliorating effects of YM-14673 on neurologic and cognitive deficits during the chronic phase of focal cerebral ischemia in rats. As far as is known, however, the clinical significance of TRH and its analogs has not been demonstrated in the treatment of ischemic stroke. The dose tolerable for patients is probably an important factor in the clinical efficacy of these compounds.

RGH-2202 {Posatirelin, (−)-(2S)-*N*-[(1S)-1-[[(2S)-2-carbamoyl-1-pyrrolidinyl]carbonyl]-3-methylbutyl]-6-oxopipecolamide}, is a TRH analog with slightly stronger CNS effects and much weaker hormonal effects than those of the parent peptide (13,14). The compound is confirmed in the clinical study to be well tolerated up to doses of 10 mg, IV, once a day for 14 days, whereas the clinical dose of TRH (Hirtonin, Takeda, Osaka, Japan; as a tartrate form) is 0.5 or 2 mg, IV, once a day for 10–21 days.

The present study was designed to compare the effects of RGH-2202 on behavioral changes during 35 days following MCA occlusion in rats with those of TRH. The test com-

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pounds were given immediately after the operation and afterward, once a day for 14 days. The effects of the compound on the course of recovery from neurologic and cognitive deficits were tested during the repeated treatment and after discontinuation of the treatment as well.

METHODS

Animals

We used male Std-Wistar rats (Japan SLC Inc., Shizuoka, Japan) weighing 250–300 g at surgery. Animals were housed in plastic cages, given food (CE2; Clea Japan Inc., Tokyo, Japan) and tapwater ad lib, and were kept in a regulated environment (24 ± 1°C, 60 ± 5% humidity), with a 12 L : 12 D light-dark cycle (light on at 0600 h).

For 5 days after the surgery, rats were given special food softened by adding water to CE2.

Surgery

Five groups of 16 rats each (MCA occlusion, RGH-2202 1 mg/kg per day, RGH-2202 3 mg/kg per day, RGH-2202 10 mg/kg per day, and TRH 10 mg/kg per day) were subjected to surgery of MCA occlusion. The rats were anesthetized with 2% halothane (Takeda), and the proximal portion of the left MCA was permanently occluded by a microsurgical technique originally developed by Tamura et al. (20) and modified by Yamamoto et al. (21) for the purpose of chronic experiments. After the temporalis muscle was retracted via a transretro-orbital approach without removal of the temporalis muscle and zygomatic arch, the animals underwent a left subtemporal craniectomy. The stem of the MCA was electrocauterized just medial to the olfactory tract and was cut to ensure the completeness of the vascular occlusion.

A sham operation (a group of 16 rats) was performed in the same manner except that MCA was not occluded.

Neurologic Tests

The neurologic deficits, hemiplegia when the rats' right legs were lifted by a bar and abnormal posture when the rats were lifted by their tails, were evaluated 7, 14, 21, 28, and 35 days after MCA occlusion according to the method of Yamamoto et al. (21). Each sign was scored using the following criteria: 0, no abnormality; 1, mild abnormality; 2, severe abnormality. Scores obtained from two signs were summed to provide an overall score (0–4).

Passive Avoidance Test

The step-through apparatus (floor 50 × 8 cm; height 18 cm) described previously (13) was used for passive avoidance learning in rats. Training trials were given 3 and 28 days after MCA occlusion. Each trial was started by placing a rat in the light compartment facing an opening into the dark compartment. After the rat moved into the dark compartment, a sliding door attached between two compartments was closed, and 5 s afterward an inescapable electric shock (0.75 mA, 50 Hz, 10 ms for 3 s) was delivered to the feet. In each trial, the latency to enter the dark compartment (step-through latency) was recorded.

In the test trials given 4, 7, 14, 21, 28, 29, and 35 days after the operation, the rat was placed in the light compartment and step-through latency was measured (cutoff time: 600 s).

Measurement of ω_3 Binding Site Densities

The degree of neural tissue damage was indirectly examined by assessing ω_3 binding site densities, which is known as a sensitive index of the quantification of brain lesions (2,5).

A total of 35 days after operation, animals were decapitated and the brains excluding the cerebellum were rapidly removed. Each brain was divided into right (intact side) and left (occluded side), frozen on dry ice, and stored at −80°C until the assay time.

The densities of ω_3 sites were measured according to the method of Schoemaker et al. (17), with slight modifications. Equilibrium binding assays were done in a final volume of 1 ml containing 0.7 ml of 50 mM Na-K phosphate-buffered saline (PBS) (181 mM Na^+, 9.5 mM K^+, 50 mM PO_4^{3-}, 100 mM Cl^-, pH 7.4), 0.1 ml of tissue homogenate (final tissue concentration of approximately 2.5 mg of original weight per milliliter of incubation medium for brain homogenates), 0.1 ml of [^{3}H]Ro5-4864 [final concentration of 3 nM (New England Nuclear, Boston, MA), specific activity 3.256 TBq/mmol] and 0.1 ml of drug solution. Incubation of the samples was at 0°C for 150 min. After incubation, membranes were collected by a Brandel cell harvester (Gaithersburg, MD) over Whatman GF/B glass fiber filters, and were subsequently washed with three 5-ml aliqots of ice-cold Na-K PBS. Retained radioactivity was counted by a liquid scintillation spectrometer (Tri-Carb model 460 CD; Packard, Downers Grove, IL). Specific binding of [^{3}H]Ro5-4864 was defined as the amount of radioactivity displaced by 100 μM diazepam. The protein content of the tissue homogenate was determined according to Lowry et al. (11) using human serum albumin as a standard.

Drug Treatment

RGH-2202 (purity: 99.7%) was obtained from Gedeon Richter Ltd. (Budapest, Hungary), and TRH was perchased from a commercial source (Peptide Institute, Inc., Osaka, Japan). They were dissolved in 0.9% saline and administered IP to the corresponding groups of rats in a volume of 0.1 ml/100 g just after the operation and thereafter once a day for 14 days. Under the same schedule, saline was given to the MCA-occlusion and sham-operation groups. Neurologic and learning tests during the period of drug (or saline) administration were carried out 30 min after treatment.

Statistics

Statistical differences among the values for individual groups were determined using Fisher's exact probability test or Williams-Wilcoxon's or Duncan's multiple range test.

RESULTS

Changes in Physiologic State and Body Weight

After MCA occlusion or sham operation, most of rats did not eat for 1–3 days, and some of them [i.e., three rats in the RGH-2202 (1 mg/kg per day)-treated group and two in the TRH (10 mg/kg per day)-treated group] never recovered and subsequently died. The death rates in both groups were similar to those commonly observed in MCA-occluded rats (21) and not statistically different from the death rate in the vehicle-treated group (Fisher's exact probability test). Therefore, the results corresponding to dying rats were excluded from subsequent data analysis.

Rats that did recover usually began to eat within 5 days after the operation, and their body weights gradually increased afterward. However, the body weight in MCA-occluded rats was significantly lower than that in sham-operated rats throughout a 35-day observation period. Repeated treatment with RGH-2202 (1, 3, and 10 mg/kg per day) and TRH (10 mg/kg per day) until day 14 lessened the decrease in body weight of MCA-occluded rats to the level of the sham-operated rats (Fig. 1).

Effect on Neurologic Deficits

Sham-operated rats exhibited few neurologic deficits; the mean score was below 1 throughout the observation period. The MCA occlusion caused neurologic deficits, which reached a maximum of 7 and 14 days after MCA occlusion and then gradually recovered. Repeated treatment with RGH-2202 (1, 3, and 10 mg/kg per day) improved the neurologic deficits in a dose-related manner. In addition, the recovery from the deficits was still advanced after the discontinuation of treatment. Thus, almost complete recovery was observed on days 28 and 35 in rats treated with 3 and 10 mg/kg per day until day 14. TRH also alleviated the neurologic deficits, but the dose of 10 mg/kg per day was of the same order of potency as that of RGH-2202 3 mg/kg per day (Fig. 2).

Effect on Disturbance of Passive Avoidance Learning

After the first training session on day 3, sham-operated rats learned passively to avoid electric shock and rarely entered the dark compartment within 600 s on days 4 and 7. Although retention of the passive avoidance response in the rats gradually declined, the second training trial on day 28 consolidated the avoidance response perfectly. In contrast, MCA-occluded rats barely acquired the passive avoidance response after the first training trial, and only partially after the second training trial (Fig. 3).

RGH-2202 (1–10 mg/kg per day) improved the disturbance of passive avoidance learning during repeated treatment and even after discontinuation of the treatment. Most of the rats that had been given 3 and 10 mg/kg per day during days 0–14 learned the passive avoidance response perfectly after the second training trial on day 28, when the drug had already been withdrawn. Similar treatment with TRH (10 mg/kg per day) also improved the disturbance of passive avoidance learning, but the potency was about three times less than that of RGH-2202.

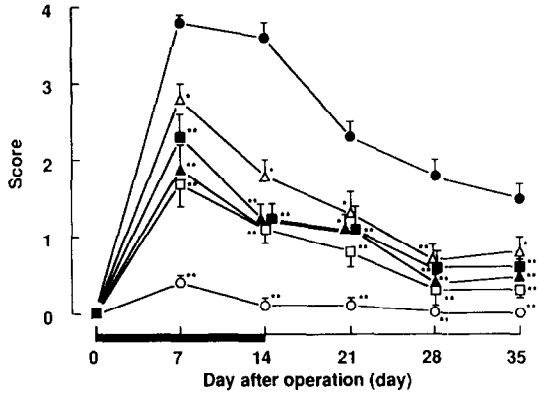

FIG. 2. Effect of RGH-2202 and TRH on neurologic deficits in MCA-occluded rats. Each value represents the mean from 13–16 rats. (○) Sham operation; (●) MCA occlusion; (△) RGH-2202 1 mg/kg per day; (▲) RGH-2202 3 mg/kg per day; (□) RGH-2202 10 mg/kg per day; (■) TRH 10 mg/kg per day. (▬The period of drug treatment: $*p < 0.05$, $**p < 0.01$ vs. MCA occlusion (Williams-Wilcoxon's multiple range test).

Effect on ω_3 Binding Site Densities

The density of ω_3 binding site in the left hemisphere (operation side) was compared with that in the right hemisphere (intact side) in each rat. The mean values of specific [^{3}H]Ro5-4864 binding to the intact side in sham operation, MCA occlusion, RGH-2202 1 mg/kg per day, RGH-2202 3 mg/kg per day, RGH-2202 10 mg/kg per day, and TRH 10 mg/kg per

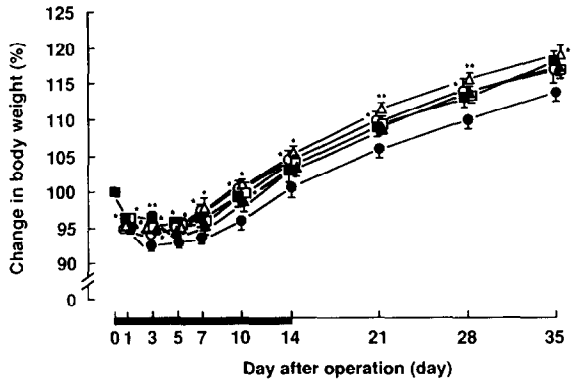

FIG. 1. The effect of RGH-2202 and TRH on body weight gain in MCA-occluded rats. Each value is the mean (±SE, n = 13–16) body weight expressed as a percentage just before the operation. (○) Sham operation; (●) MCA occlusion; (△) RGH-2202 1 mg/kg per day; (▲) RGH-2202 3 mg/kg per day; (□) RGH-2202 10 mg/kg per day; (■) TRH 10 mg/kg per day. The groups initially weighed 275.3 ± 2.5, 269.6 ± 2.9, 268.7 ± 2.5, 269.1 ± 2.1, 268.3 ± 1.6, and 265.4 ± 1.6 g, respectively. (▬The period of drug treatment: $*p < 0.05$, $**p < 0.01$ vs. MCA-occlusion (Duncan's multiple range test).

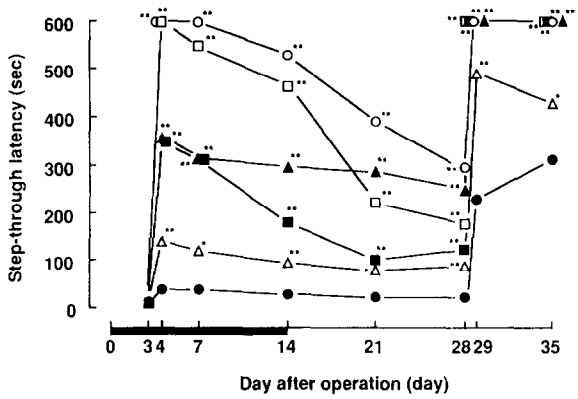

FIG. 3. Effect of RGH-2202 and TRH on passive avoidance learning in MCA-occluded rats. Each value represents the median from 13–16 rats. (○) Sham operation; (●) MCA occlusion; (△) RGH-2202 1 mg/kg per day; (▲) RGH-2202 3 mg/kg per day; (□) RGH-2202 10 mg/kg per day; (■) TRH 10 mg/kg per day. (▬The period of drug treatment: $*p < 0.05$, $**p < 0.01$ vs. MCA occlusion (Williams-Wilcoxon's multiple range test).

TABLE 1

EFFECT OF RGH-2202 AND TRH ON ω_3 BINDING SITE DENSITIES IN MCA-OCCLUDED RATS

Group	Dose (mg/kg/per day IP)	% Increase
Sham-operation	–	38.7 ± 5.5
MCA-occlusion	–	84.9 ± 12.1
RGH-2202	1	60.7 ± 8.1
	3	77.4 ± 10.4
	10	62.7 ± 10.4
TRH	10	61.3 ± 8.6

Results are expressed as the percent increase of ω_3 site densities in the left hemisphere compared with those in the right hemisphere. Each value is the mean ± SE from 13 to 16 rats.

day groups were 159 ± 5, 158 ± 4, 160 ± 4, 156 ± 4, 157 ± 4, and 168 ± 4 fmol/mg protein, respectively. The nonspecific binding in each group was 31–34% of the total binding.

A slight increase in ω_3 binding site densities of the operation side (38.7%) was observed even in the sham-operated rats. MCA occlusion induced much more of an increase in the ω_3 site (84.9%) compared with sham operation. Repeated treatment with RGH-2202 (1–10 mg/kg per day) or TRH (10 mg/kg per day) during days 0–14 was inclined to alleviate an increase in ω_3 site densities of the left hemisphere in MCA-occluded rats, although the effect was not dose-related and not statistically significant (Table 1).

DISCUSSION

Some TRH analogs are known to alleviate biochemical and functional changes in animal models of ischemia (10,15,18, 19,21,22). In particular, Yamamoto et al. (21) first examined the drug effects during a chronic phase of cerebral ischemia following MCA occlusion in rats, and demonstrated that the subsequent neurologic and cognitive deficits were ameliorated by repeated treatment with YM-14673 (once a day for 22 days). In the present study, RGH-2202 and TRH itself (once a day for 15 days) improved the behavioral deficits as well, indicating that the anti-ischemic activity may be inherent in this series of peptides. We also found that a recovery from the deficits was still advanced after discontinuation of the drug treatment: namely, the neurologic deficits were almost completely recovered by day 28 in rats treated with RGH-2202 (3 and 10 mg/kg per day) and TRH (10 mg/kg per day) during days 0–14, although the deficits were still evident in vehicle-treated rats. In addition, the drug-treated rats were superior to the vehicle-treated ones in acquiring a passive avoidance response after the second training session on day 28, when drugs had already been withdrawn. Moreover, drug treatment was inclined to lessen the lesion size of the occluded hemisphere determined by ω_3 site labeling 35 days after the operation. These results suggest that early-stage treatment with TRH or its analogs for a few weeks may improve neurologic and cognitive deficits following certain types of cerebral ischemia, and also promise a favorable prognosis.

RGH-2202 was about three times more potent than TRH in improving the behavioral deficits after MCA occlusion. The results coincide with the previous observation (13,14) that RGH-2202 is two to five times more potent than TRH in facilitating avoidance performance in poor learning, haloperidol-treated, and internal capsule-lesioned animals. Askanas et al. (1) and Casabona et al. (3) also reported that RGH-2202 exerted a trophic influence on cultured neurons at smaller concentrations than those of TRH. Such correspondence between present and precedent data suggests that the beneficial effects of the peptides in the focal ischemia model may be related to facilitating or trophic effects on CNS neurons. Cerebral blood flow has also been considered to be important in determining neuronal damage in a region of "penumbra" after MCA occlusion (12,15,18). RGH-2202 caused a more sustained, although weaker, increase in cerebral blood flow in the rat cerebral cortex than TRH (unpublished observation), which may contribute at least partly to the functional improvement by the compound.

Despite the beneficial effects of TRH and its analogs in MCA-occluded animals, the clinical efficacy of the peptides has not yet been confirmed in the treatment of ischemic desease. Certainly, some animal studies using other ischemic models failed to demonstrate their improving effects. For example, TRH had no effect, or worse, on neurologic deficits in the ischemic gerbil model (7,8). Faden (6) also failed to observe an improving effect of TRH in a canine model of embolic stroke. Therefore, whether the peptides are clinically useful may depend on the type of ischemic disease. Another important factor as to clinical efficacy of the peptides may be their dosage and treatment period tolerable for patients. Clinical dosing of TRH (Hirtonin, Takeda; as a tartrate form) is 0.5 2 mg once a day for 10–21 days. On the other hand, RGH-2202 is confirmed in the clinical study to be well tolerated up to dosing 10 mg once a day for 14 days. In addition, RGH-2202 was about three times more potent than TRH in improving neurologic and cognitive deficits in the rat MCA occlusion model. These results indicate a strong possibility that RGH-2202 exhibits clinical efficacy for certain types of ischemic diseases compared with the parent peptide. It would be valuable to know whether RGH-2202 is clinically significant in the treatment of functional deficits after cerebral ischemia.

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