CNS Drug Reviews
Vol. 4, No. 1, pp. 25–41

Taltirelin Hydrate (TA-0910): An Orally Active Thyrotropin-Releasing Hormone Mimetic Agent with Multiple Actions

Kiyoshi Kinoshita, Michio Yamamura, Juko Sugihara, Mamoru Suzuki, Yuzo Matsuoka

Pharmaceutical Development Research Laboratory, Tanabe Seiyaku Co., Ltd., Saitama 335-8505, Japan

Key Words: Disturbance of consciousness—Memory impairment—Motor dysfunction—TA-0910—Taltirelin hydrate—Thyrotropin-releasing hormone-mimetic agent

INTRODUCTION

Thyrotropin-releasing hormone (TRH; L-pyroglutamyl-L-histidyl-L-prolinamide) was first isolated from the hypothalamus as a neurohormone that stimulates the release of thyroid-stimulating hormone (TSH) and prolactin (4,5,8). Later, diverse distribution of this peptide and its receptor was demonstrated in various other regions of the central nervous system (CNS) (7,58,64,69,70). Apart from its endocrine action, TRH exerts several CNS actions, including an increase in locomotor activity, antagonism of reserpine-induced hypothermia, and antagonism of pentobarbital-induced sleep (25,77). Furthermore, pharmacological studies have revealed amelioration by TRH of depression, circulatory shock, disturbances in consciousness, memory impairment and motor dysfunction in animal models of CNS diseases (12,13,17,23–25,48,50,72,77). Based on these preclinical observations, the therapeutic potential of TRH was tested and demonstrated in clinical trials in patients with CNS dysfunction (18).

Clinical studies showed therapeutic effects of TRH in patients with loss of consciousness, motor disturbances, and memory impairment (6,18,51,60,65). These effects of TRH were short-lived, however, because of its rapid metabolic degradation (3). Furthermore, clinical use of TRH has been limited because it has endocrine actions at doses much lower than those that affect CNS. A TRH mimetic with a long-lasting CNS activity and a low endocrine potency might, therefore, be a better thera-

Address correspondence and reprint requests to Dr. K. Kinoshita, Pharmaceutical Develop ment Res. Lab., Tanabe Seiyaku Co., LTD., Kawagishi 2-2-50,, Toda-shi, Saitama 335-8505, Japan. Fax: (81) 48-433 -8161.

Fig. 1. Chemical structures of taltirelin hydrate and TRH.

peutic agent for these diseases (53). Over the past two decades, various types of TRH analogs have been synthesized and tested in attempts to develop useful therapeutic agents (18,19,53), but none of them has so far been successfully marketed.

Taltirelin hydrate (TA-0910, taltirelin; Fig. 1) is a novel, orally effective TRH mimetic (67,73). With respect to its CNS stimulant actions, taltirelin is 10 to 100 times more potent and about eight times longer-lasting than TRH (40–42,73). In contrast, the TSH-releasing activity of this compound was five to ten times lower than that of TRH (54). Recent clinical studies have demonstrated that taltirelin arrests the course of the disease and ameliorates ataxia in patients with spinocerebellar degeneration, a progressive neurodegenerative disease (21,38), thus confirming the results of our pharmacological studies (41,42) and lending support to its predicted usefulness as a therapeutic agent. This review summarizes the available preclinical and clinical studies with taltirelin.

CHEMISTRY

Exogenously administered TRH is rapidly metabolized by degrading enzymes, such as pyroglutamyl peptidase I (EC 3.4.19.3) and II (EC 3.4.19.6), that exist in blood and brain, respectively (58). Therefore, the chemical structure of taltirelin, (–)-*N*-([S]-hexahydro-1-methyl-2,6-dioxo-4-pyrimidinylcarbonyl)-L-histidyl-L-prolinamide tetrahydrate (Fig. 1) (67), was designed to protect the pyroglutamyl peptide bond of TRH from enzymatic hydrolysis.

Taltirelin is a white, odorless, crystalline powder, with a molecular weight of 477.47 ($C_{17}H_{23}N_7O_5 \cdot 4H_2O$). It is soluble in water, acetic acid and ethanol and slightly soluble in methanol and acetonitrile, but practically insoluble in ether and chloroform.

Fig. 2. Time course of degradation of taltirelin and TRH in the blood and brain homogenate of male rats. Each point represents the mean ± S.E.M. of three animals. Reproduced with permission from ref. 46.

PHARMACOLOGY

Selectivity for TRH Receptors

The ability of taltirelin (up to 6.3 μM) to compete for binding of the radioligands of 31 types of receptors and ion channels was investigated. According to displacement studies in rat cortical membranes, the only ligand displaced by taltirelin was [^{3}H]methyl-TRH, the specific radioligand for TRH receptors. The affinity of taltirelin for TRH receptors (K_i = 120 nM) was ten times lower than that of TRH in crude membranes prepared from rat whole brain (15). This analog was hardly degraded in blood samples for up to 3 h but degraded in brain homogenates with a half-life of 64.4 min, which was about eight times longer than the half-life of TRH (Fig. 2) (46). Its high stability in the body and low affinity for TRH receptors should make taltirelin a more potent and long-lasting CNS agent than TRH (Fig. 3).

Behavioral Pharmacology

Taltirelin is expected to act as a CNS stimulant and a TRH receptor agonist. We determined the potential for its use in the treatment of motor dysfunction, memory im - pairment, and consciousness disturbances in animal disease models.

Anti-Ataxic Action

We evaluated the anti-ataxic action of taltirelin in three different types of motor dysfunction: the rolling mice Nagoya (RMN), which shows genetic dysfunction of the

Fig. 3. Potent central nervous system (CNS) and weak endocrine actions of taltirelin.

cerebellum, brain stem, and/or striatum (42,55–57,71); rats with chemical degeneration of the inferior olive induced by intraperitoneally (i.p.) administered 3-acetylpyridine (3-AP, 40 mg/kg) (11,49,66); and rats with lesions of the thoracic spinal cord induced by mechanical compression (20).

In RMN, oral (p.o.) taltirelin (1 to 10 mg/kg) markedly decreased the fall index in walking (Fig. 4) (41). This index represents the weakness of motor coordination in the hindlimbs. There was a marked reduction in local cerebral glucose utilization (LCGU) in the ventral tegmental area (VTA) of RMN. Taltirelin restored the lowered LCGU.

Fig. 4. Effects of single oral administration of taltirelin and thyrotropin-releasing hormone (TRH) on the fall index (number of falls per spontaneous motor activity in 10 min) in rolling mouse Nagoya ($n = 11$). $^{*}P < 0.05$, $^{**}P < 0.01$ compared with distilled water-treated control (ANOVA followed by Dunnett's multiple comparison test). Reproduced with permission from ref. 41.

The stimulation of VTA is, therefore, likely to be involved in the mechanism of action of taltirelin (42).

3-AP-induced motor incoordination is called "mud-walking" (49). Taltirelin (3 or 10 mg/kg/d p.o.) markedly ameliorated the ataxic gait in this model (41). Restoration of motor incoordination was completely counteracted by pretreatment with MK-801, an NMDA receptor antagonist (44). It is conceivable, therefore, that the antiataxic effect of taltirelin in 3-AP-treated rats is mediated by NMDA receptors.

In spinal-compressed rats there were a transient motor and sensory dysfunction of the hind limbs (20). The ataxia in these rats gradually recovered in 30 to 50 d. Taltirelin (3 or 10 mg/kg/d p.o.) markedly accelerated the recovery from motor dysfunction (41).

TRH ameliorated ataxia in rolling mice and 3-AP-treated rats at doses of 100 and 300 mg/kg/d. Thus, taltirelin was about 100 times more potent than TRH in its antiataxic effect by oral administration.

Amelioration of Memory Impairment

To evaluate the effects of taltirelin on memory impairment, we studied the one-trial passive avoidance response (light-dark box) in mice with CO_2-induced anoxia, active avoidance response (shuttle box) in rats with basal forebrain (BF)-lesions, and delayed alternation task (T-maze) in scopolamine-treated rats. The BF possesses cholinergic cell bodies innervating the cerebral cortex (52). The CO_2-induced amnesia was ameliorated by taltirelin (3 to 30 mg/kg p.o.) in a dose-dependent manner in the passive

Fig. 5. Effects of taltirelin and thyrotropin-releasing hormone (TRH)on the 180-s-delayed alternation task in rats treated with scopolamine ($n = 23$). Taltirelin and TRH were orally administered 40 and 20 min before the trial, respectively. Scopolamine (0.1 mg/kg) was intraperitoneally administered 20 min before the trial. Random choice level (50%) is represented by a horizontal broken line. C: distilled water-treated control. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with the value of scopolamine-treated control (Tukey-type multiple comparison test).

avoidance test (75). In the active avoidance test, taltirelin (0.3 to 3 mg/kg p.o.) prevented the memory impairment caused by BF-lesions in a dose-dependent manner. This drug (0.3 to 3 mg/kg p.o.) also reversed the scopolamine-induced memory impairment in the T-maze alternation test (Fig. 5) (75). On the contrary, orally administered TRH produced no improvement in any of these tests. It can be concluded that by oral route taltirelin but not TRH ameliorates certain types of memory impairment.

Arousal Action

Orally or intravenously administered taltirelin shortened the duration of sleep induced by pentobarbital in rodents in a dose-dependent manner (73,74). Moreover, the drowsy pattern of the cortical electroencephalogram (EEG) was changed to the arousal pattern in pentobarbital-anesthetized rabbits by taltirelin (0.3 mg/kg i.v.) or TRH (3 mg/kg i.v.) (73). These drugs also activated spontaneous EEGs in awake rabbits.

We analyzed the effect of taltirelin on the disturbed consciousness in mice with an experimental concussion (50,68). After the concussion, mice transiently lost consciousness and righting reflex. Intravenously administered taltirelin shortened the time for the recovery of the righting reflex (RR-time) in a dose-dependent manner with a minimum effective dose of 0.03 mg/kg (K. Kinoshita, unpublished data). TRH was about ten times less effective than taltirelin in shortening the RR-time. These observa-

tions suggest that taltirelin has a therapeutic potential in the treatment of consciousness disturbances.

Other actions

Antidepressant activity of taltirelin was studied in the behavioral despair and reserpine models (9,10,61,62). Taltirelin (0.003 to 0.3 mg/kg i.v. and p.o.) shortened the immobility time during forced swimming in a dose-dependent manner (unpublished). Moreover, taltirelin antagonized reserpine-induced hypothermia in mice at a dose of 0.3 mg/kg p.o. or 0.03 mg/kg intraperitoneally (i.p.) (73). Thus, taltirelin exerts antidepressant action as well.

Effects of taltirelin on spinal reflex responses were compared with those of TRH in C_1-spinal rats. Taltirelin (0.3 and/or 1 mg/kg i.v.) increased the amplitude of mono- and polysynaptic reflex potentials and augmented withdrawal flexor reflexes in a dose-dependent manner (Fig. 6) (40). The TRH-induced augmentation of the reflex responses was weak and short lived. Intraduodenally administered taltirelin (10 mg /kg) but not TRH also potentiated the withdrawal flexor reflex. Therefore, orally administered taltirelin may be useful in the treatment of functional spinal disorders.

Neurochemical Pharmacology

TRH stimulates the cholinergic and monoaminergic system in the CNS (53). We studied, therefore, the effects of taltirelin on neurochemical markers.

Neurotransmitter Release

Stimulatory action on the cholinergic system: Taltirelin (0.1 to 1 mg /kg i.p.) caused a dose-dependent increase in extracellular acetylcholine (ACh) levels in the hippocampus of freely moving rats (Fig. 7) (43). In terms of potency and duration of action, TRH was less effective than taltirelin (Fig. 7). In rats treated with γ-butyrolactone, a nerve impulse flow blocker, accumulation of ACh in the cerebral cortex and hippocampus was suppressed by taltirelin (1 or 3 mg /kg i.p.) (43). Moreover, in physostigmine (1 mg/kg i.p.)-treated rats, this drug (at the same doses) increased the accumulation rate of ACh in these regions. TRH (30 mg /kg i.p.) also suppressed the accumulation of ACh in the hippocampus of γ-butyrolactone treated rats. These results suggest that taltirelin accelerates the turnover of ACh at the cholinergic nerve terminals.

Stimulatory action on the monoaminergic system: In a 3-h microdialysis study in rats, the extracellular levels of dopamine (DA) and its metabolites, 3,4-dihydroxyphenylacetic and homovanillic acids, in the nucleus accumbens and corpus striatum were increased by taltirelin (1 to 10 mg /kg i.p.) (16). TRH (30 mg/kg i.p.) was less potent in this respect. Taltirelin (10 mg/kg i.p.) also increased the contents of L-3-dihydroxy-phenylalanine, a precursor of DA and norepinephrine, in the nucleus accumbens and corpus striatum. Methoxy-4-hydroxyphenylglycol, a norepinephrine metabolite, was also increased in the frontal cortex and hypothalamus (16). Moreover,

Fig. 6. Effects of intravenous administration of taltirelin and thyrotropin-releasing hormone (TRH) on the flexor reflex in spinal rats ($n = 4$). $^{*}P < 0.05$, $^{**}P < 0.01$ compared with saline-treated control (Dunnett's type multiple comparison test followed by the Kruskal-Wallis test). Reproduced with permission from ref. 60.

accumulation of 5-hydroxytryptophan, a serotonin precursor, and of 5-hydroxyindoleacetic acid, a serotonin metabolite, was demonstrated in the nucleus accumbens or corpus striatum. These results suggest that taltirelin stimulates not only the DA system, but also norepinephrine and serotonin systems.

Increase in Cerebral Metabolism and Blood Flow

Effects of taltirelin and TRH on LCGU and cerebral blood flow (CBF) were studied using positron emission tomography (PET) in lightly anesthetized monkeys. LCGU and CBF were measured by the use of [^{18}F]fluoro-2-deoxy-D-glucose and

Fig. 7. Effects of intraperitoneal administration of taltirelin and thyrotropin-releasing hormone (TRH) on *in vivo* acetylcholine (ACh) release from the hippocampus in conscious and freely moving rats. ACh release was expressed as the percentage of the average of four consecutive values before drug administration ($n = 4$). $^{*}P < 0.05$, $^{**}P < 0.01$ compared with saline-treated control (one-way ANOVA followed by Dunnett's test). Reproduced with permission from ref. 43.

$[^{15}O]H_2O$, respectively, by conventional methods. In various areas of the cerebrum and cerebellum taltirelin (1 mg/kg i.v.) and TRH (3 mg/kg i.v.) increased LCGU 20% to 40% and less than 20%, respectively (K. Tamura, personal communication). Likewise, in various cerebral regions there was an increase (more than 80%) in CBF for 90 min after taltirelin (0.03 to 0.3 mg/kg i.v.) (K. Tamura, personal communication). The increase in CBF by TRH (0.3 or 3 mg/kg i.v.) was transient and small (30%). These results support the activation of cerebrum and cerebellum by taltirelin.

Neurotrophic Action

After experimental injury, endogenous TRH levels increase in the spinal cord (14,63). TRH increases the neuronal perikaryal area and maximum diameter in cultured spinal ventral horn neurons (2). Moreover, TRH stimulates neurite outgrowth in the ventral spinal cord (33).

In *in vitro* studies using the ventral spinal cord explant cultures of rat embryos, taltirelin (10^{-14} to 10^{-4} M) increased neurite outgrowth in a concentration-dependent manner (34). The minimum effective concentration was 10^{-12} M.

The effect of taltirelin on the process of neuronal damage was evaluated in the motoneurons of neonatal rats. Neuronal damage was induced by transection of the sciatic nerve. Fourteen-day-treatment with taltirelin (2 and 10 mg/kg/d i.p.) significantly prevented the death of motoneurons in lumber 4 – 6 segments following axotomy (35). These *in vitro* and *in vivo* observations suggest that taltirelin exerts neurotrophic effects in the CNS.

General Pharmacology

General pharmacology

In rats and mice, taltirelin (≥ 10 mg/kg p.o.) caused CNS-stimulant effects, including hyperlocomotion and stereotypy (1). In the digestive system, the drug at oral doses of 3 to 10 mg/kg increased gastric juice secretion and accelerated small intestinal transit (30). In the cardiovascular system at therapeutically effective doses of taltirelin the blood pressure in anesthetized animals tended to increase. All these general pharmacological properties of taltirelin were shared by TRH.

TSH-Releasing Action

Taltirelin at 2.75 μmol/animal (~4.2 mg/kg p.o.) and TRH at 0.275 μmol/animal (~0.46 mg/kg p.o.) produced almost the same level of secretion of TSH in rats (54). The elevated TSH by taltirelin decreased to the control level within 6 h. Thus, the TSH-releasing activity of taltirelin is five to ten times weaker than that of TRH.

PHARMACOKINETICS AND METABOLISM

The absorption, distribution, metabolism, and excretion of [^{14}C] taltirelin (3 mg/kg p.o.) were studied in rats and dogs. Following oral administration to rats, the plasma level of radioactivity reached the maximal level (C_{max}) of 157 ng. eq/ml at 1 h (T_{max}) (45). The plasma half-life ($t_{1/2}$) was 119 min. The radioactivity level decreased substantially at 24 h after administration of taltirelin, and radioactivity was excreted mainly in the urine within 48 h after administration (45). In dogs, C_{max}, T_{max}, and $t_{1/2}$ of plasma radioactivity were 508 ng. eq/ml, 1.5 h, and 146 min, respectively. The intestinal absorption rates of taltirelin were 9 and 21%, and the values of bioavailability were 3.9 and 18.5% in rats and dogs, respectively. There were no significant sex-related differences in these pharmacokinetic parameters (45).

Taltirelin was absorbed from all regions of the small intestine (45). Radioactivity levels of [^{14}C]taltirelin (3 mg/kg) reached a peak at 30 min to 3 h in the liver, kidney, spleen, lung, bloody, and skin in rats. The unchanged taltirelin level in the brain, a

target organ of its pharmacological effect, reached maximum levels (T_{max} = 1 h) of 135 to 364 pg/g and then gradually decreased (46). The unchanged taltirelin, however, was not detected in the brain at 6 h after dosing.

There were two metabolites, (–)-*N*-[(S)-hexahydro-1-methyl-2,6-dioxo-4-pyrimidinylcarbonyl]-L-histidyl-L-proline and (S)-hexahydro-1-methyl-2,6-dioxo-4-pyrimidinylcarboxylic acid, together with unchanged taltirelin in plasma and urine of either rats or dogs (45). These metabolites suggest that taltirelin is metabolized similarly to TRH (58).

TOXICOLOGY

In acute toxicology studies, the LD_{50} values for orally administered taltirelin were > 5000 mg/kg in mice and rats. The LD_{50} values for intravenously administered taltirelin were > 2000 mg/kg in mice and 799 and 946 mg/kg in male and female rats, respectively (22). Hyperactivity, tremor, and Straub tail were observed in rodents, and also wet-dog shaking in rats. In dogs, the minimal lethal dose was > 2000 mg /kg p.o. One out of two female dogs receiving 500 mg/kg i.v. died on the day following administration; there were no deaths in male and female dogs treated with taltirelin 1000 mg/kg i.v. Vomiting, hyperactivity, salivation, and transient tachycardia were observed in dogs after oral or intravenous administration of taltirelin at doses ≥ 500 mg/kg (22).

Oral subacute and chronic toxicity (13- and 52-week) studies were conducted in rats and dogs. The "no observable adverse effect level" of taltirelin was 30 mg /kg/d in rats (31). At 300 mg/kg/d, there was a decrease in the body weight gain in male rats and elongation of estrous cycle in female rats. The effects of taltirelin in dogs were studied at doses of 0.5, 5, and 50 mg/kg/d for 13 weeks or 0.15, 1.5, and 15 mg/kg/d for 52 weeks. Decreases in food intake and body weight gain, and an increase in the thyroid weight with no histopathological changes, were observed at 5 mg/kg/d (32). The no observable adverse effect levels in 13- and 52-week studies in dogs were, therefore, 0.5 and 1.5 mg/kg, respectively. All of the above changes in rats and dogs were alleviated or abolished during a 4-week recovery period.

To study the effect of the drug on reproduction and development, we conducted fertility, teratogenicity, perinatal, and postnatal studies in rats. A teratogenicity study was also carried out in rabbits. Animals were given taltirelin at 0.15 to 15 mg /kg/d by oral administration. There was no teratogenic, lethal, or growth retardation effects in the fetuses (26). Moreover, taltirelin did not exert any toxic effects in dams or embryos (27–29). Furthermore, there were no toxic signs on viability, growth, physical differentiation, functional and behavioral development, or reproductive performance in F_1 offspring, or development of F_2 fetuses (29). The no-toxicity dose level of taltirelin was, therefore, 15 mg/kg/d for reproductive function of parent animals and for their offspring.

There was no evidence of oncogenic potential with taltirelin (76). In antigenicity and mutagenicity studies, this drug caused no abnormalities (F. Ariyuki, unpublished).

In addition, taltirelin causes neither physical nor psychic dependence (T. Asahi, personal communication).

CLINICAL TRIALS

Clinical Phase I study

Twelve healthy male volunteers received single oral doses of taltirelin (0.5 to 40 mg/person). Serum concentration of taltirelin increased in a dose-dependent manner, reached a maximal level at 3 to 5 h, and then decreased gradually with a $t_{1/2}$ of about 2 h (36). Blood pressure and serum levels of TSH, tri-iodothyronine (T_3), and thyroxine (T_4) were increased in a dose-dependent manner. Headache, abdominal discomfort, pyrosis, and poor appetite were reported at doses $\geq$ 10 mg/person. Pulse rate, body temperature, and electrocardiogram (ECG) were in the normal range. Other biochemical variables, including blood and urinary examinations, did not change. Moreover, the hematological indices were also unaffected (36).

In the repeated oral dose study, taltirelin was administered to twenty healthy male volunteers at 5 mg/person once a day or 2.5 mg/person twice a day for 14 d (37). Blood pressure, pulse rate, and body temperature were normal. No problematic findings in ECG or blood and urinary examinations were reported during or after taltirelin administration. TSH, T_3, T_4, and prolactin levels in serum showed significant changes, but these values were within normal ranges. Slight headache and nausea were observed as subjective symptoms. Pharmacokinetic parameters of taltirelin, such as C_{max}, T_{max}, and $t_{1/2}$, were almost identical between the first and last administrations (37). These findings indicate that taltirelin does not accumulate during repeated administration to men.

Clinical Phase II Study

Sixty patients with spinocerebellar degeneration were enrolled in a 6-week, randomized double-blind, placebo-controlled 2-way crossover study of taltirelin (21). After a 2-week observation period, patients were divided into two groups. One group was given 20 mg of taltirelin twice a day for the first 2 weeks and then placebo for the next 2 weeks. Another group was given placebo for the first 2 weeks and taltirelin for the remaining 2 weeks. The evaluation was based on neurological scoring of the gait, speech ability, and tests for coordination of extremities in finger-nose, tapping-point, knee-pat, and knee-heel tests.

The global improvement rating in the taltirelin group was superior to placebo ($P = 0.0394$; Wilcoxon's rank sum test) (21). Individual analysis showed trends of superiority in neurotic scores in the finger-nose test and tapping-point test. Taltirelin was also better than placebo in spontaneity and overall mental symptoms (spontaneity: $p = 0.0448$; overall: $p = 0.0296$; Wilcoxon's rank sum test). Moreover, this drug

showed trends for less orthostatic hypotension or autonomic symptoms. Adverse reactions affected mainly digestive organ disorders, including gagging, nausea, and stomach discomfort. All adverse reactions were mild to moderate and disappeared during the treatment period and/or after withdrawal.

Clinical Phase III Study

Patients with spinocerebellar degeneration ($n = 427$) were enrolled for > 6 months in a double-blind, randomized, placebo-controlled study of taltirelin for evaluation of clinical efficacy (arrest of disease course and amelioration of ataxia) and safety (38). Patients were randomly assigned to oral taltirelin (5 mg/patient twice a day, $n = 213$) or matching placebo ($n = 214$) for 28 to 52 weeks. The evaluation was based on approximately the same neurological scoring as used in the phase II study.

At the twenty-eighth week, the global improvement rating in the treatment group was superior to that in the placebo group ($p < 0.001$; Wilcoxon test) (38). The cumulative aggravating rate (Kaplan – Meier method) of the taltirelin group (27.7%) was significantly lower than that of the placebo group (41.7%) (difference between the 2 groups: –14.0%; 95% confidence interval: –24.1 to –4.1%). The overall improvement rating of ataxia in the taltirelin group was significantly superior to that of the placebo group ($p < 0.004$; Wilcoxon's test). The cumulative aggregating rate of ataxia in the taltirelin group (27.1%) was significantly lower than that of the placebo group (39.4%) (difference between the 2 groups: –12.3%; 95% confidence interval: –22.2 to –2.4%) (38). The incidence of adverse reactions in the taltirelin-treated group (14.1% of patients) was almost the same as that in the placebo group.

Taken together, these clinical studies suggest that taltirelin is effective in arresting the disease course and ameliorating ataxia in patients with spinocerebellar degeneration.

CONCLUSIONS

Pharmacological analysis revealed potent and long-lasting multiple CNS actions of taltirelin. These CNS actions may be brought about through cerebral TRH receptors. Although the affinity of taltirelin for TRH receptors was about ten times lower than that of TRH, this compound is more stable than TRH in the body. Sustained effective concentrations of taltirelin in the CNS can, therefore, explain the more potent and long-lasting CNS effect of taltirelin.

On the other hand, with respect to its TSH-releasing action, taltirelin is less potent than TRH. This paradox, that taltirelin exhibits a more potent CNS activity and less potent endocrine activity, can be explained in terms of "metabolic stability and uneven bioavailability" to the pituitary gland as compared to the CNS (53). The low affinity of taltirelin for TRH receptors should make this TRH-mimetic a weaker endocrine agent than TRH (Fig. 3). Furthermore, TSH release is regulated by a potent

negative feedback system involving thyroid hormones (47). This negative feedback system should also suppress the endocrine potential of taltirelin.

The data described in this review show that taltirelin is effective in the treatment of patients with spinocerebellar degeneration. The new drug aplication for taltirelin as an anti-ataxic drug in the treatment of this disease has been filed. Its CNS stimulant action suggests a therapeutic potential for the drug in patients with other CNS dysfunctions, including consciousness disturbances and memory impairment.

Acknowledgments: The authors would like to thank Drs. A. Saito and S. Takeyama for offering helpful suggestions. The authors also would like to thank Drs. I. Fukuchi, T. Fukushima, S. Furuuchi, Y. Honma, T. Inui, R. Ishida, K. Matsumoto, T. Nagao, H. Ono, M. Yoshikawa, and Messrs. H. Asai, T. Asahi, S. Chishima, T. Fujitsuka, M. Inamasu, K. Kawashima, Y. Kodama, H. Nakagawa, M. Takahashi, K. Tamura, T. Tanaka, and Ms. Kawashima, A. Kono, K. Maeda, Y. Watanabe for their contributions.

REFERENCES

1. Asahi T, Yamaguchi K, Kato M, Kinoshita K, Yamamura M, Matsuoka Y. General pharmacology of taltirelin hydrate (TA-0910). I. Effects on gross behavior and the central nervous system. *Pharmacometrics* 1997;54:349–360.
2. Banda RW, Means ED, Scherch HM. Trophic effect of thyrotropin-releasing hormone in murine ventral horn neuronal cultures. *Ann NY Acad Sci* 1989;553:588–589.
3. Bassiri RM, Utiger RD. Metabolism and excretion of exogenous thyrotropin-releasing hormone in humans. *J Clin Invest* 1973;52:1616–1619.
4. Bøler J, Enzmann F, Folkers K, Bowers CY, Shally AV. The identity of chemical and hormonal properties of the thyrotropin releasing hormone and pyroglutamyl-histidyl-proline amide. *Biochem Biophys Res Commun* 1969;37:705–710.
5. Bowers CY, Friesen HG, Hwang P, Guyda HJ, Folkers K. Prolactin and thyrotropin release in man by synthetic pyroglutamyl-histidyl-prolinamide. *Biochem Biophys Res Commun* 1971;45:1033–1041.
6. Brooks BR. A summary of the current position of TRH in ALS therapy. *Ann NY Acad Sci* 1989;553:431–461.
7. Brownstein MJ, Palkovits M, Saavedra JM, Bassiri RM, Utiger RD. Thyrotropin-releasing hormone in specific nuclei of rat brain. *Science* 1974;185:267–269.
8. Burgus R, Dunn TF, Desiderio D, Vale W, Guillemin R. Derivés polypeptidiques de syntheses doués d'activité hypophysiotropic TRF. Nouvelles observations. *C R Acad Sci* (*Paris*) 1969;269:1870–1873.
9. Classen V, Davies JE. Potentiation of tricyclic antidepressants of weight loss caused by amphetamine in rats. *Acta Physiol Pharmacol Nedel* 1969;15:37–40.
10. Costa E, Garratini S, Valzilli L. Interactions between reserpine, chlorpromazine, and imipramine. *Experimentia* 1960;16:461–463.
11. Desclin JC, Escubi J. Effects of 3-acetylpyridine on the central nervous system of the rat, as demonstrated by silver methods. *Brain Res* 1974;77:349–364.
12. Faden AI, Jacobs TP, Holaday JW. Thyrotropin-releasing hormone improves neurologic recovery after spinal trauma in cats. *New Eng J Med* 1981;305:1063–1067.
13. Faden AI, Jacobs TP, Smith MT. Thyrotropin-releasing hormone in experimental spinal injury: Dose response and late treatment. *Neurology* 1984;34:1280–1284.
14. Faden AI, Hill TG, Kubek MJ. Changes in TRH immunoreactivity in spinal cord after experimental spinal injury. *Neuropeptides* 1986;7:11–18.

15. Fukuchi I, Asai T, Yamamura M, Matsuoka Y, Ishida R. Neurochemical study of TA-0910, a new T RH analog (5); effects of chronic treatment on TRH, muscarinic acetylcholine (mACh), and D-2 dopa mine receptors in rat brain. *Jpn J Pharmacol* (Suppl 1) 1993;61:249.
16. Fukuchi I, Asahi T, Kawashima K, et al. Effects of taltirelin hydrate (TA-0910), a novel thy rotropin-releasing hormone analog, on *in vivo* dopamine release and turnover in rat brain. *Arzneim-Forsch/Drug Res* 1998;48:353–359.
17. Fukuda N, Saji Y, Nagawa T. Behavioral and EEG alterations with brain stem compression an d effect of thyrotropin-releasing hormone (TRH) in chronic cats. *Folia Pharmacol Japon* 1979;75:321–331.
18. Griffiths EC. Clinical application of thyrotropin-releasing hormone. *Clin Sci* 1987;73:449–457.
19. Guiloff RJ. Use of TRH analogues in motoneuron disease. *Ann NY Acad Sci* 1989;553:399–421.
20. Hashimoto T, Fukuda N. Effect of thyrotropin-releasing hormone on the time I-course of neu rologic recovery after spinal cord injury in the rat. *Jpn J Pharmacol* 1990;53:479–486.
21. Hirayama K, Tashiro K, Takayanagi T, Takahashi K, Ogawa N, Arai K. The clinical evaluation of TA-0910 in spinocerebellar degeneration (SCD): A double blind cross-over comparative stud y vs. placebo. *J Clin Therap Med* 1997;13:4133–4167.
22. Hishida N, Kuse H, Yamamura T, Noguchi M, Kawai Y, Hori M. Acute toxicity studies of taltir elin tetrahydrate in mice, rats, and dogs. *J Toxicol Sci* (Suppl II) 1997;22:27–334.
23. Holaday JW, D'Amato RJ, Faden AI. Thyrotropin-releasing hormone improves cardiovascula r function in experimental endotoxic and hemorrhage shock. *Science* 1981;213:216–218.
24. Holaday JW, Ruvia BA, Faden AI. Thyrotropin releasing hormone improves blood pressure an d survival in endotoxic shock. *Eur J Pharmacol* 1981;74:101–105.
25. Horita A, Carino MA, Lai H. Pharmacology of thyrotropin- releasing hormone. *Annu Rev Pharmacol Toxicol* 1986;26:311–332.
26. Imahie H, Kobayashi T, Imado H, Inui T, Ariyuki F, Asano Y. Reproductive and developmen tal toxicity studies of taltirelin hydrate. (1) Fertility study in rats by oral administration. *J Toxicol Sci* (Suppl II) 1997;22:371–379.
27. Imahie H, Kobayashi T, Nishida A, Imado H, Asano Y. Reproductive and developmental toxi city studies of taltirelin hydrate. (2) Teratogenicity study in rats by oral administration. *J Toxicol Sci* (Suppl II) 1997;22:381–394.
28. Imahie H, Nishida A, Imado H, Asano Y. Reproductive and developmental toxicity studie s of taltirelin hydrate. (3) Teratogenicity study in rabbits by oral administration. *J Toxicol Sci* (Suppl II) 1997;22:395–403.
29. Imahie H, Koguchi A, Kobayashi T, Asano Y. Reproductive and developmental toxicity st udies of taltirelin hydrate. (4) Perinatal and postnatal study in rats by oral administration. *J Toxicol Sci* (Suppl II) 1997;22:405–417.
30. Inamasu M, Kikkawa H, Nishiyama S, et al. General pharmacology of taltirelin hydrate (TA -0910). 2. Effects on respiratory and cardiovascular systems, autonomic nervous system and smooth m uscle, digestive system, renal function and somatic nervous system. *Pharmacometrics* 1997;54:361–381.
31. Inui T, Fujiwara T, Susami M, et al. Repeated dose toxicity studies of taltirelin tetrah ydrate (TA-0910) by oral administration to rats. *J Toxicol Sci* (Suppl II) 1997;22:335–356.
32. Inui T, Yuasa H, Adachi T, Kawai Y, Kudow S. Repeated dose toxicity studies of taltirelin tetrahydrate (TA-0910) with oral administration to dogs. *J Toxicol Sci* (Suppl II) 1997;22:357–369.
33. Iwasaki Y, Kinoshita M, Ikeda K, Takamiya K, Shiojima T. Trophic effect of various neuropep tides on the cultures ventral spinal cord of rat embryo. *Neurosci Lett* 1989;101:316–320.
34. Iwasaki Y, Ikeda K, Shiojima T, Kinoshita H. TRH analogue, TA-0910 (3-methyl-(s)-5,6-dihydr oorotyl-L-histidyl-L-prolinamide) enhances neurite outgrowth in rat embryo ventral spinal cord *in vitro*. *J Neurol Sci* 1992;112:147–151.
35. Iwasaki Y, Shiojima T, Kinoshita M. TRH analog, TA-0910 (3-methyl-(s)-5,6-dihydroorotyl-L- histidyl-L-prolinamide) rescues motor neurons from axotomy-induced cell death. *Neurol Res* 1998;19:613–616.
36. Kainuma H, Morikawa S, Tagawa K, et al. Clinical phase I study of TA-0910: Oral single dose s tudy. *J Clin Therap Med* 1997;13:2501–2516.
37. Kainuma H, Morikawa S, Tagawa K, et al. Clinical phase I study of TA-0910: Oral repeated dose study. *J Clin Therap Med* 1997;13:2517–2532.

38. Kanazawa I, Satoyoshi E, Hirayama K, et al. Clinical evaluation of taltirelin hydrate (TA -0910) in patients with spinocerebellar degeneration: A multi-center double-blind comparative study w ith placebo. *J Clin Therap Med* 1997;13:4169–4224.
40. Kinoshita K, Nagao T, Ono H. Effects of TA-0910, an orally active TRH analog, on the spina l reflex in spinal rats. *Neuropharmacology* 1994;33:1183–1188.
41. Kinoshita K, Fujitsuka T, Yamamura T, Matsuoka Y. Effects of TA-0910, a novel orally acti ve thyrotropin-releasing hormone analog, on the gait of ataxic animals. *Eur J Pharmacol* 1995;274:65–72.
42. Kinoshita K, Watanabe Y, Asai H, Yamamura M, Matsuoka Y. Anti-ataxic effects of TRH and its analogue, TA-0910, in Rolling mouse Nagoya by metabolic normalization of the central tegmenta l area. *Br J Pharmacol* 1995;116:3274–3278.
43. Kinoshita K, Kawashima K, Kawashima Y, Fukuchi I, Yamamura M, Matsuoka Y. Effect of TA-0910, a novel thyrotropin-releasing hormone analog, on *in vivo* acetylcholine release and turnover in rat brain. *Jpn J Pharmacol* 1996;71:139–145.
44. Kinoshita K, Watanabe Y, Yamamura M, Matsuoka Y. TRH receptor agonists ameliorate 3-acet ylpyridine-induced ataxia through NMDA receptors in rats. *Eur J Pharmacol* 1998;343:129–133.
45. Kodama H, Furuuchi S, Takahashi M, Sugihara J, Yoshikawa M. Disposition of taltirelin. (1) Absorption, distribution, metabolism and excretion in rats and dogs. *Xeno Metab Dispos* 1997;12:460–474.
46. Kodama H, Fukushima T, Chishima S, Sugihara J, Yoshikawa M. Disposition of taltirelin. (3) The transfer into the brain and brain distribution in rats. *Xeno Metab Dispos* 1997;12:483–490.
47. Köhrle J, Brabant G, Hesch RD. Metabolism of the thyroid hormones. *Hormone Res* 1987;26:58–78.
48. Kurihara E, Fukuda N, Narumi S, Matsuo T, Saji S, Nagawa Y. Effects of thyrotropin-releasi ng hormone tartrate (TRH-T) and its main metabolite histidyl-proline diketopiperazine on the walkin g ataxia in rolling mouse Nagoya. *Jpn Pharmacol Ther* 1985;13:49–56.
49. Llinas R, Walton K, Hillman DE. Inferior olive: Its role in motor learning. *Science* 1979;190:1230-1231.
50. Manaka S, Fuchinoue T, Kondo T, Hori T. Effects of thyrotropin-releasing hormone tartrate on consciousness disturbance; preclinical report. *Brain Nerve* 1977;29:1075–1081.
51. Mellow AM, Dunderland T, Cohen MR, Nurphy DL. Acute effect of high-dose thyrotropin rele asing hormone infusion in Alzheimer's disease. *Psychopharmacology* 1989;98:403–407.
52. Mesulam M-M, Mufson EJ, Wainer BH, Levey AI. Central cholinergic pathways in the rats: An overview based on an alternative nomenclature (Ch1-Ch6). *Neuroscience* 1983;10:1185–1201.
53. Metcalf G. Regulatory peptides as a source of new drugs: The clinical prospects for analo gues of TRH which are resistant to metabolic degradation. *Brain Res Rev* 1982;4:389–408.
54. Moriyasu M, Nasu M, Honda H, Sakamoto T, Yamamura M, Matsuoka Y. Effect of (–)- *N*-[(S)-hexahydro-1-methyl-2,6-dioxo-4-pyrimidinylcarbonyl]-L-histidyl-L-prolinamide (TA-0910), a new TRH an alog, on plasma levels of TSH and thyroid hormones in rats. *Folia Pharmacol Jpn* 1996;107:285–297.
55. Muramoto O, Ando K, Kanazawa I. Central noradrenaline metabolism in cerebellar ataxic mice. *Brain Res* 1982;237:387–395.
56. Nakayama T, Nagai Y. Alterations in local cerebral glucose metabolism and endogenous thyrotropin-releasing hormone levels in rolling mouse Nagoya and effect of thyrotropin-releasing hormone tartrate. *Jpn J Pharmacol* 1996;72:241–246.
57. Nishimura Y. The cerebellum of rolling mouse Nagoya. *Adv Neurol Sci* 1975;19:670–672.
58. O'Leary R, O'Connor B. Thyrotropin-releasing hormone. *J Neurochem* 1995;65:953–963.
59. Oliver C, Eskay RL, Ben-Jonathan N, Porter JC. Distribution and concentration of TRH in t he rat brain. *Endocrinology* 1974;95:540–546.
60. Pitts LH, Ross A, Chase GA, Faden AI. Treatment with thyrotropin-releasing hormone (TRH) in patients with traumatic spinal cords injuries. *J Neurotrauma* 1995;12:235–243.
61. Porsolt RD, Bertin A, Jalfre M. Behavioural despair in mice: A primary screening test for antidepressants. *Arch Int Pharmacodyn* 1977;229:327–336.
62. Porsolt RD, LePichon M, Jalfre M. Depression: a new animal model sensitive to antidepr essant treatment. *Nature* 1977;266:730–732.
63. Salzman SK, Knight PB, Hirofuji E, Llados-Eckman C, Beckman AL, Winokur A. Spinal cord im - munoreactive TRH is altered after local traumatic injury. *Peptides* 1987;8:247–250.
64. Sharif NA. Quantitative autoradiography of TRH receptors in discrete brain regions of different mammalian species. *Ann NY Acad Sci* 1989;553:147–175.

65. Sobue I, Matsuoka Y, Katoh K, Sakuma A. TRH therapy of ataxia in patients with SCD. In: Sobu e I, ed. *TRH and Spinocerebellar Degeneration*. Amsterdam: Elsevier, 1986;173–188.
66. Sukin D, Skedros DG, Beales M, Stratton SE, Lorden JF, Oltmans GA. Temporal sequence of m otor disturbances and increased cerebellar glutamic acid decarboxylase activity following 3- acetylpyridine lesions in adult rats. *Brain Res* 1987;426:82–92.
67. Suzuki M, Sugano H, Matsumoto K, Yamamura M, Ishida R. Synthesis and central nervous syst em actions of thyrotropin-releasing hormone analogues containing a dihydroorotic acid moiety. *J Med Chem* 1990;33:2130–2137.
68. Tanaka K, Ogawa N, Asanuma M, Kondo Y. Thyrotropin-releasing hormone prevents abnormalit ies of cortical acetylcholine and monoamine in mice following head injury. *Regul Peptides* 1997;70:173–178.
69. Winokur A, Utiger RD. Thyrotropin-releasing hormone: Regional distribution in rat brain . *Science* 1974;185:265–267.
70. Winokur A, Manaker S, Kreider MS. TRH and TRH receptors in the spinal cord. *Ann NY Acad Sci* 1989;553:314–324.
71. Yamaguchi T, Kato M, Fukui M, Akazawa K. Rolling mouse Nagoya as a mutant animal model of b asal ganglia dysfunction: Determination of absolute rates of local cerebral glucose utilizat ion. *Brain Res* 1992;298:38–44.
72. Yamamoto M, Shimizu M. Effect of YM-14673, a new thyrotropin-releasing hormone analogue, o n ataxic gait in cytosine arabinoside-treated mice. *Eur J Pharmacol* 1989;166:545–547.
73. Yamamura M, Kinoshita K, Nakagawa H, Tanaka T, Maeda K, Ishida R. Pharmacological study o f TA-0910, a new thyrotropin-releasing hormone (TRH) analog. (1) Effects on the central nervo us system by oral administration. *Jpn J Pharmacol* 1990;53:451–461.
74. Yamamura M, Kinoshita K, Nakagawa H, Ishida R. Pharmacological study of TA-0910, a new th yrotropin-releasing hormone (TRH) analog. (3) Inhibition of pentobarbital anesthesia. *Jpn J Pharmacol* 1991;55:69–80.
75. Yamamura M, Kinoshita K, Nakagawa H, Ishida R. Pharmacological study of TA-0910, a new th yrotropin-releasing hormone (TRH) analog. (4) Effects on experimental memory impairment in mice and rats. *Jpn J Pharmacol* 1991;55:251–253.
76. Yamamura T, Nishimura T, Kuwamura Y, Inui T, Aughton P, Kawai Y. Oncogenicity studies of taltirelin tetrahydrate (TA-0910) by oral administration in CD-1 mice and CD rats. *J Toxicol Sci* (Suppl II) 1997;22:419–430.
77. Yarbrough GG. On the neuropharmacology of thyrotropin releasing hormone (TRH). *Prog Neurobiol* 1979;12:291–312.