Review article

Thyrotropin-releasing hormone: role in the treatment of West syndrome and related epileptic encephalopathies

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Abstract

Thyrotropin-releasing hormone (TRH) has been successfully used for treating children with neurologic disorders including epilepsy. The effectiveness of TRH and a TRH analog has been reported in West syndrome, Lennox–Gastaut syndrome, and early infantile epileptic encephalopathy that were intractable to anticonvulsants and adrenocorticotrophic hormone (ACTH). However, the peptide has not been widely studied as a treatment of intractable epilepsy outside Japan. TRH is safe in children and effective in some cases of West syndrome and Lennox–Gastaut syndrome. TRH is considered as a possible new strategy for treating West syndrome and Lennox–Gastaut syndrome prior to ACTH therapy, especially for the patient with an infection, immunosuppression, or severe organic lesions in the brain. The mechanisms of its antiepileptic action may differ from those of other antiepileptic drugs. One possibility is that TRH may act as an antiepileptic through a kynurenine mechanism, considering that kynurenic acid acts as an antagonist on the N-methyl-d-aspartate receptor complex.

Keywords: Thyrotropin-releasing hormone; West syndrome; Lennox–Gastaut syndrome; Cerebrospinal fluid; Kynurenine

1. Introduction

Thyrotropin-releasing hormone (TRH; 1-pyroglutamyl-1-histidyl-1-prolineamide), the first hypothalamic-releasing hormone to be isolated, is widely distributed throughout the central nervous system (CNS) [1–4]. Since the tripeptide structure of TRH makes it vulnerable to enzymatic degradation, various analogs have been synthesized and evaluated [2]. TRH and its analogs have been reported to regulate the actions of classical neurotransmitters, such as serotonin, noradrenaline, dopamine, and acetylcholine [4]. In Japan, TRH has been used successfully to treat children with neurologic disorders such as cerebellar ataxia, spinal muscular atrophy, and spinocerebellar degeneration [5–8]. TRH has a neurotrophic effect on motor neurons and it may influence motor neurons through serotonergic pathways [6–8]. Evidence of a possible relationship between epileptic seizures, electroencephalographic activity, and the effectiveness of TRH has accumulated [9,10]. In spite of the introduction of new drugs, seizures in a number of children with epilepsy remain uncontrolled. Thus, a potent, yet safer therapy is needed. Adrenocorticotrophic hormone (ACTH), which has been used for treating children with intractable epilepsy, such as West syndrome and Lennox–Gastaut syndrome, is occasionally associated with serious adverse effects, including brain shrinkage, subdural hematoma, immunosuppression, body weight gain, and hypertension [11–13]. Among these, rapid brain shrinkage during the first year of life should not be neglected when considering the remarkable development of the brain during this period. ACTH may affect the development of the brain and its long-term efficacy in seizure disorders has been challenged [13]. In this article, the role of TRH in the treatment of West syndrome and related epileptic encephalopathies is highlighted, and the author’s personal experience and opinion are mentioned. The details of clinical trials of DN-1417 (an analog of TRH) for intractable epilepsy have been reviewed earlier [9].

2. Experimental studies of antiepileptic action of TRH

Several mechanisms for the antiepileptic action of TRH have been proposed according to the results of experimental studies as reviewed previously [9]. The results of animal experiments suggested that TRH modulates the release and turnover of monoamines, especially dopamine and serotonin, which are in principle inhibitory neurotransmitters in the brain, and that this results in antiepileptic action. In an
experimental study on El mice with several kinds of monoamine abnormality, it was found that the hippocampal TRH system may play an inhibitory role in seizures, whereas the striatal TRH system may be important as to seizure susceptibility.

Kindling is a model for human epilepsy that consists of periodic electrical or chemical low intensity stimulation that produces a gradual increase in neuronal after-discharge and eventually a generalized seizure is obtained. Electrical stimulation of the brain induces change in TRH level and TRH produces an antiepileptic effect in kindled animals. TRH is reported to have two independent effects in the dentate gyrus, an increase in cellular excitability and a decrease in synaptic function, and the latter is considered to be related to the anticonvulsant effects on kindling. Both an electroconvulsive shock and kindled seizures resulted in marked elevation of TRH in specific limbic areas, such as the hippocampus, amygdala, and the piriform, cingulated, and frontal cortices. TRH receptors were found to be densely concentrated within these regions in several species. Moreover, kindled seizures induced a considerable increase in the TRH level in the hippocampus, with a reduction of TRH receptor binding. Recently, Kubek [10] has referred to the mechanisms of the antiepileptic effects of TRH in experimental animals in his excellent review.


TRH has been used in a number of epilepsies, but so far studies have mainly concentrated on West syndrome and Lennox–Gastaut syndrome. A trial of TRH for the treatment of these syndromes is considered to be warranted because both are devastating and no definitive treatment has been established. An outstanding contribution concerning TRH therapy for children with intractable epilepsy was undertaken by Matsumoto et al. [14] who investigated the positive and adverse effects of TRH in severely epileptic children, including those with Lennox–Gastaut syndrome and West syndrome. In their study, the subjects were divided into two groups; 33 patients treated with ACTH and 31 with TRH. In the TRH group, complete control of seizures was achieved in 53.7% of patients with West syndrome within 4–16 days of initiation of the TRH therapy, and marked electroencephalogram (EEG) improvement was observed in 61.5%. In four of the seven responding cases, seizures recurred within 1 week to 3 months after their cessation. In the ACTH group, seizure cessation was observed in 75% of the West syndrome cases, and marked EEG improvement was observed in 60% of cases. Considering West syndrome alone, they reported that a relapse of seizures occurred in 67% of the TRH group and 78% of the ACTH group.

In addition, Matsumoto et al. [15] reported factors that influence the responsiveness to TRH therapy in 38 children with severe epilepsy. Those factors analyzed were: sex, age, etiology, neurologic abnormalities, seizure type, seizure frequency, EEG findings, duration of TRH therapy, and serum human growth hormone, prolactin, and thyroid-stimulating hormone levels before and after TRH therapy. The authors found that the serum prolactin level was significantly correlated with the effectiveness of the TRH therapy; basal serum prolactin decreased significantly, especially in good responders; and basal serum prolactin was especially elevated in patients with West syndrome, who had a greater response to TRH therapy. The mechanism triggering the decrease in prolactin after TRH therapy is not clear.

Takeuchi et al. [9,16] studied the efficacy of TRH-tartrate (TRH-T) in 16 children with West syndrome, 11 with Lennox–Gastaut syndrome, and one with early infantile epileptic encephalopathy intractable to antiepileptic drug therapy and to ACTH. TRH-T was administered intravenously and intramuscularly at a single dose of 0.05 mg kg\(^{-1}\) per day for 4 weeks. The subjects were classified into three groups based on the frequency of seizures and the EEG effects: cessation of seizures and seizure discharges for more than 1 year (very effective group), reduction of seizures and/or seizure discharges (effective group), and no changes in the frequency of seizures or discharges (not effective group). There were eight cases in the very effective group, six in the effective group, and 14 in the not effective group (Table 1). The patients in the very effective group stopped having seizures, including infantile spasms, tonic seizures, atypical absence, atonic seizures, and myoclonic seizures, within 11 days to 3 months after initiation of the TRH therapy, and no seizures occurred thereafter for at least 2 years (Table 2). The 16 patients with West syndrome comprised five cases in the very effective group (Figs. 1 and 2), three in the effective group, and eight in the not effective group. The 11 patients with Lennox–Gastaut syndrome were subdivided into three cases in the very effective group, three in the effective group, and five in the not effective group. In a case with Lennox–Gastaut syndrome, the non-convulsive status of atypical absence promptly reacted to TRH administration. In this study, the relatively long duration of the effect of TRH after the therapy is stressed (Table 2).

Besides the antiepileptic effect of TRH, enhancement of psychic activities, such as psychomotor activity, facial

<table>
<thead>
<tr>
<th></th>
<th>WS (no. of cases)</th>
<th>LGS (no. of cases)</th>
<th>EIEE (no. of cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very effective</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Effective</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Not effective</td>
<td>8</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1
Results of TRH therapy for 16 patients with West syndrome (WS), 11 with Lennox–Gastaut syndrome (LGS), and one with early infantile epileptic encephalopathy (EIEE) intractable to antiepileptic drug therapy and to ACTH.
expression, and motivation, was also noted in patients with intractable epilepsy [9,16]. This non-antiepileptic effect of TRH is very valuable in practice. The non-anticonvulsive effects of TRH, namely not suppression, but activation of the CNS, should not be underestimated in the treatment of epilepsy.

4. Adverse effects of TRH therapy

Transient urinary retention, irritability, sleepiness, worsening of involuntary movements, tremor, tachycardia or bradycardia, appetite loss, nausea, and vomiting have all been described in patients treated with TRH. However, the adverse effects were infrequent and minimal [9,16].

5. Recommended protocol for TRH therapy

According to previous results and the author’s own experience [5,6,8,9,16,17], the following is recommended as a TRH therapy protocol for intractable epilepsy in children. Intravenous or intramuscular administrations are superior to oral administration. On the first day of therapy, TRH-T is administered intravenously by drip infusion at the dose of 0.05 mg kg$^{-1}$ per day. It is recommended that EEG recording be continued for 1 h after the TRH administration to observe changes in EEG findings and possible acute adverse effects of TRH. The same dose of the peptide is then administered intramuscularly once daily at about 10:00 a.m., so as not to disturb the wake–sleep cycle. In principle, the therapy is given for a total of 4 weeks, with

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Table 2

Clinical presentations and courses of patients of very effective group

<table>
<thead>
<tr>
<th>No.</th>
<th>Age at TRH therapy</th>
<th>Sex</th>
<th>AEDs previously given</th>
<th>Epilepsy</th>
<th>Duration of TRH therapy</th>
<th>Effect of TRH therapy</th>
<th>Relapse of seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 years</td>
<td>F</td>
<td>VPA, PH1, PB</td>
<td>LGS</td>
<td>28 days</td>
<td>1 month</td>
<td>5 years</td>
</tr>
<tr>
<td>2</td>
<td>5 years</td>
<td>M</td>
<td>VPA, ZNS, CZP</td>
<td>LGS</td>
<td>28 days</td>
<td>3 months</td>
<td>3 years</td>
</tr>
<tr>
<td>3</td>
<td>7 years</td>
<td>M</td>
<td>VPA, CZP, PB</td>
<td>LGS</td>
<td>28 days</td>
<td>1 month</td>
<td>2 years</td>
</tr>
<tr>
<td>4</td>
<td>5 months</td>
<td>F</td>
<td>VPA, CZP, PB</td>
<td>WS</td>
<td>28 days</td>
<td>2 months</td>
<td>2 years</td>
</tr>
<tr>
<td>5</td>
<td>1 year</td>
<td>M</td>
<td>CZP, ZNS</td>
<td>WS</td>
<td>12 days</td>
<td>2 months</td>
<td>5 years</td>
</tr>
<tr>
<td>6</td>
<td>5 months</td>
<td>M</td>
<td>VPA, ZNS</td>
<td>WS</td>
<td>56 days</td>
<td>11 days</td>
<td>3 years</td>
</tr>
<tr>
<td>7</td>
<td>1 year</td>
<td>F</td>
<td>VPA, ZNS, CZP</td>
<td>WS</td>
<td>28 days</td>
<td>1 month</td>
<td>2 years</td>
</tr>
<tr>
<td>8</td>
<td>7 months</td>
<td>F</td>
<td>VPA, CZP</td>
<td>WS</td>
<td>28 days</td>
<td>3 months</td>
<td>2 years</td>
</tr>
</tbody>
</table>

* AED, antiepileptic drug; WS, West syndrome; LGS, Lennox–Gastaut syndrome; EIEE, early infantile epileptic encephalopathy; CZP, clonazepam; PB, phenobarbital; PH1, phenytoin; VPA, valproate; ZNS, zonisamide; After initiation; Time lag from TRH initiation to seizure control.

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Fig. 1. EEG changes during TRH therapy (West syndrome of very effective group). (A) Before TRH therapy. (B) Ten days after initiation of TRH therapy. (C) Three weeks after initiation of TRH therapy.
a 1-week interval between the two treatment phases (Fig. 3). EEG is recorded once a week and the patients continue to receive the previous doses of their antiepileptic drugs. The efficacy of serial TRH administration, in terms of the frequency of clinical seizures and changes in EEG discharges, is evaluated at the end of the course and at least 3 months after initiation of the TRH therapy. The efficacy of TRH therapy should be observed for a longer observation period (at least 3 months) than in the case of ACTH, mainly because of the differences in the mechanisms of their antiepileptic actions.

6. Neurochemical studies on the mechanism of the antiepileptic effect of TRH

Recently, Takeuchi et al. [17] demonstrated that TRH therapy increased cerebrospinal fluid (CSF) concentration of kynurenine in patients with intractable epilepsy. They investigated 14 children (six males and eight females), aged 5 months to 16 years, with intractable epilepsy. The diagnosis was West syndrome in eight patients, Lennox–Gastaut syndrome in three, severe myoclonic epilepsy in two and localization-related epilepsy in one. The disorders of the patients remained uncontrolled after treatment by conventional antiepileptic drugs, such as valproate, clonazepam, phenytoin, phenobarbital, and zonisamide. TRH-T was administered according to the protocol described above. Before TRH therapy, and 2 weeks after initiation of the therapy, CSF was collected by means of lumbar puncture between 10:00 am and noon, with parental understanding and consent. The following monoamine-related substances: tryptophan, 5-hydroxytryptophan, 5-hydroxyindole-acetic acid, kynurenine, tyrosine, homovanillic acid, 3-methoxy-4-hydroxyphenyl glycol, and 3-O-methyl-DOPA were measured using high-performance liquid chromatography coupled with a high-sensitivity electrochemical detector array (Neurochem, ESA, Bedford, MA) [17–20]. In this study, the patients were classified into two groups based on the frequency of seizures: more than a 50% reduction.
of seizure frequency (effective group) and less than 50% reduction of seizure frequency or no change in frequency of seizures (ineffective group). Two weeks after the initiation of TRH therapy, seven patients including four patients with West syndrome, two with Lennox–Gastaut syndrome, and one with localization-related epilepsy showed more than 50% reduction of seizure frequency. There was no reduction in seizure frequency in the other seven patients. Among the monoamine-related substances in CSF, only kynurenine was significantly increased after TRH therapy. There were no significant changes in other monoamine-related substances after TRH therapy. Concerning the correlation of elevated kynurenine concentrations with seizure frequency, it is noteworthy that seven patients of the effective group showed elevated kynurenine concentrations in their CSF. There was no improvement in the seizures of three patients who did not show elevated CSF kynurenine. This is the first study to reveal that TRH therapy increases CSF concentrations of kynurenine in human neurological disorders.

7. Kynurenine pathway

Kynurenine and kynurenic acid are present in the extracellular fluid within the CNS, which can synthesize kynurenic acid. As a broad-spectrum antagonist of excitatory amino acid receptors, kynurenic acid can antagonize electrophysiological responses to N-methyl-D-aspartate (NMDA) and kainic acid receptor agonists, and to a lesser degree, quisqualate receptor agonists. Kynurenic acid acts at both the glycine allosteric site and the agonist recognition site on the NMDA receptor complex [21–23]. Moreover, brain concentrations of kynurenic acid are correlated with kynurenine concentrations [21,24,25]. Decreased kynurenine levels have been demonstrated in the CSF of children with infantile spasms [26]. TRH may have antiepileptic action through a kynurenine pathway (Fig. 4).

On the other hand, the kynurenine pathway has been highlighted in the light of recent neuroimmunology. Increased enzymatic degradation of tryptophan is found in diseases that are associated with chronic stimulation of Th1-mediated immunity, such as human immunodeficiency virus-1 (HIV-1) infection, malignant disease, and autoimmune disease [27]. Indoleamine 2,3-dioxygenase (IDO) is the rate-limiting enzyme in the catabolism of tryptophan. IDO production by syncytiotrophoblast or macrophages has been demonstrated to result in the inhibition of T-cell proliferation due to tryptophan depletion [28]. The degradation of tryptophan positively correlates with indicators of immune activation in macrophages, such as neopterin and soluble cytokine receptors, which confirms that cytokines increase IDO activity as estimated by the ratio of kynurenine to tryptophan concentration [29].

8. Conclusions

TRH is considered to be a possible new strategy for treating West syndrome and Lennox–Gastaut syndrome prior to ACTH therapy, especially for the patient with an infection, immunosuppression, or severe organic lesions in the brain. In practice, enhancement of psychic activities, such as psychomotor activity, facial expression, and motivation, is a very valuable addition to the antiepileptic effect of TRH. Further research, including clinical and experimental studies on the kynurenine pathway, is required to elucidate the mechanism of the anti-epileptic action of TRH, which may lead to a better understanding of the pathophysiology of epilepsy itself.

![Fig. 4. Kynurenine pathway.](image-url)
Acknowledgements

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References