Hy CRF mRNA levels. The response to ADX was greatly amplified in the AP as compared to the Hy. CRF increased ACTH secretion and POMC mRNA levels in cultured pituitary adenoma or nonadenoma cells from patients with Cushing's disease. Inhibitory effects of dexamethasone on ACTH secretion and POMC mRNA levels in non-adenoma cells were greater than those in adenoma cells. Therefore, adenomas resist the inhibitory effect of dexamethasone on POMC mRNA levels and ACTH secretion.

6. CRF test

Patients with hypothalamic hypopituitarism had ACTH responses to CRF, while patients with primary hypopituitarism had no ACTH response to CRF. The patients in both groups had no ACTH response to hypoglycemia. This result suggests that the response of the pituitary corticotroph to CRF is preserved after hypothalamic dysfunction.

In patients with Cushing's syndrome of adrenal origin, low ACTH and high cortisol levels did not respond to CRF. In Cushing's disease, elevated plasma ACTH and cortisol levels increased after CRF injection. In patients with ectopic ACTH syndrome, plasma ACTH responses to CRF were variable. The CRF test also was useful for evaluating the recovery of the HPA axis after remission of hypercortisolism. The recovery of cortisol response to CRF (9-12 months) was delayed as compared with that of ACTH (6-9 months). Lowered levels of CRF in plasma and cerebrospinal fluid returned to the normal range 3-6 months after the remission.

7. Immuno-HPA axis

Many publications in recent years have focused on the interrelationship between the immune system and the HPA axis. For example, 1) inhibitory effect of glucocorticoids on the immune response, 2) receptors for POMC-derived peptides on mononuclear cells, 3) gene expression of POMC mRNA in mononuclear cells and secretion of POMC-like peptides, 4) the modulation of the HPA axis by cytokines.

In our study, plasma ACTH levels increased 2 hours after ip injection of recombinant interleukin-1 (IL-1)-α and -β in rats. AP ACTH and Hy CRF contents decreased after IL-1 administration. The levels of AP POMC mRNA and Hy CRF mRNA slightly, but significantly, increased 2 hours after IL-1 injection.

On the other hand, IL-1α and -β did not alter ACTH secretion from cultured rat AP cells after 3 hours of incubation, but stimulated ACTH secretion after 15 hours of incubation. Therefore, the stimulatory effects of IL-1 on ACTH release from AP cells are not as fast as the action of CRF. These results suggest that the acute stimulation of ACTH secretion induced by IL-1 in vivo is unlikely to be due to a direct action of IL-1 at the pituitary level, but is probably the result of activation of Hy CRF release. In addition, chronic stimulation by IL-1 may act at both AP and Hy levels to increase ACTH secretion. The direct effect of IL-1 or POMC gene expression, if any, seems to be minimal.

4. Neuropeptides and Neurological Diseases

a. Spinocerebellar Degeneration and Neuropeptides

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Spinocerebellar degeneration (SCD) is a degenerative disorder of the nervous system mainly involving the cerebellar system. Ataxia is its main clinical symptom and sign. In 1983, Sobue et al (1) reported that thyrotropin releasing hormone (TRH), one of the hypothalamic peptides, improved ataxic
symptoms of SCD. In the present report, we further studied the efficacy of TRH and another peptide, ceruletide, on the various symptoms and signs of SCD.

1. Effects of TRH on limb ataxia of SCD

Effects of acute and chronic administration of TRH on ataxia of the upper limbs of SCD patients were analysed using a position sensor system.

Subjects consisted of 12 SCD patients (7 males and 5 females). The age ranged between 46 and 71 years old (average 56.1 years old). Based upon the classification of subtypes of SCD, 2 were Menzel type of olivopontocerebellar atrophy (OPCA), 4 were sporadic OPCA, 2 were Shy-Drager syndrome, 2 were striato-nigral degeneration, 1 was dentato-rubropallidoluysian atrophy (DRPLA) and 1 was Joseph's disease.

The patients were instructed to touch a target 0.5m apart in front of them with their index fingers as soon as possible when they heard a trigger sound. The positions of the index finger, wrist, elbow and shoulder were recorded with a position sensor system. The movement was analysed measuring the following indexes. Reaction time (RT) was a period between the trigger sound and the start of the movement. Movement time (MT) was a period between the start and the end of the movement. Touch time (TT) was the sum of RT and MT. Correction time (CT) was a period between the beginning of slow approach of the finger near the target and the end of the movement. \( V_{max} \) meant maximum movement velocity. \( CP \) was the movement trajectory of the index finger during CT, and \( CD \) was the straight distance between the starting point of CT and the end of it. In the previous report, we showed that RT, MT, CT and \( CP/CD \) were larger and \( V_{max} \) was smaller in SCD patients than in normal controls.

After intravenous administration of 2 mg TRH, RT, MT, CT, \( V_{max} \) did not show any changes. \( CP/CD \) was significantly decreased \( (p<0.05) \) between 30 and 75 minutes after the TRH treatment. As a chronic treatment, the patients were given TRH intramuscularly in a dose of 1mg daily for 14 days. After the treatment, MT and CT were slightly decreased and \( V_{max} \) was slightly increased. However, these changes were not statistically significant. \( CP/CD \) again showed significant decrease \( (p<0.05) \) after the treatment. \( CP/CD \) was considered to be an index showing quantity of surplus movement of the index fingers near the target. Therefore, the fact that \( CP/CD \) was significantly decreased after both acute and chronic administration of TRH seemed to indicate that this drug improved ataxic symptoms of the upper limbs, such as dysmetria, hypermetria and kinetic tremor in SCD.

2. Effects of oral administration of TRH on ataxia of SCD

TRH was administered orally in a dose of 24mg daily for longer than 6 months to 22 patients with SCD. 15 were males and 7 were females. The age ranged between 31 and 66 years old (average 46.6 years old). Based upon the classification of subtypes of SCD, 1 was late cerebellar cortical atrophy (LCCA), 14 were Menzel type of OPCA and 7 were sporadic OPCA. Ataxia improvement rating of standing, gait, speech and writing and global improvement rating were evaluated at the end of 1, 2, 3, 6, 9, 12, 24, 36 and 48 months of treatment.

The result of global improvement rating revealed that responses rated as moderately improved and slightly improved were approximately 10 to 20% between 2 and 12 months after the start of treatment. The rate of the patients rated as moderately aggravated and slightly aggravated were steadily increased after 3 months. More than 30% of patients were rated as no change even at 12 and 24 months after the start of the treatment.

These results seemed to indicate that this drug does not have such effect as improving the ataxic symptoms in SCD for a long period, but has usefulness in preventing the aggravation of the symptoms.

3. Effects of TRH on autonomic symptoms of SCD

TRH treatment markedly improved orthostatic hypotension in one of the patients with Shy-Drager syndrome. The patient was a 53-year-old male with a 12 year history of ataxia, extrapyramidal symptoms and autonomic symptoms, such as urinary disturbance, orthostatic syncope, hyposweating, constipation and impotence. TRH was administered intramuscularly in a dose of 4 mg daily for 10 days.

Postural changing test before the treatment revealed that the systolic blood pressure of the patient was decreased by 50mmHg when he sat up from the supine position. When he stood up, the
systolic blood pressure was further decreased by 30mmHg, and he complained of faintness. On the other hand, after the TRH treatment, the decrease of his blood pressure was limited to 25mmHg from the supine to sitting position and 20mmHg from the sitting to standing position. The result of norepinephrine infusion test indicated that supersensitive pressor response to norepinephrine became much milder after TRH treatment.

4. Effects of ceruletide on involuntary movements of SCD

Ceruletide is a kind of decapeptides which has a similar chemical structure to cholecystokinin (CCK). Effects of this peptide on the involuntary movements seen in a case of dentatorubropallidoluysian atrophy (DRPLA) was studied. Ceruletide was given intramuscularly in a dose of 0.8 μg/kg body weight once a week for 3 weeks. Facio-orolingual dyskinesia and choreic movement of limbs were moderately decreased after the treatment. In evaluation using abnormal involuntary movement scale (AIMS), total score was decreased from 21 at the start of administration to 14 after the treatment.

CONCLUSIONS

1. Acute intravenous and chronic intramuscular administration of TRH improved ataxic symptoms of upper limbs of SCD in evaluation using a position sensor system.
2. It was suggested that long-term oral administration of TRH prevented aggravation of ataxic symptoms of SCD.
3. TRH treatment improved autonomic symptoms in a case of Shy-Drager syndrome.
4. It was suggested that ceruletide might improve the involuntary movements of SCD.

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REFERENCES


b. Alzheimer's Disease

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Much attention has recently been focused on neuropeptide levels in the brain of patients with Alzheimer's disease in addition to classical neurotransmitters such as acetylcholine and monoamines. Although all neuropeptides have not been proved to play a role in the neurotransmission, investigations on abnormalities in neuropeptides in Alzheimer's disease may provide tools for the differential diagnosis and therapy as well as the elucidation of the mechanism of Alzheimer's disease. Several peptides in the brain lack a peripheral effect as a hormone, but have been reported to exert important functions in the central nervous system. The present paper describes changes in peptides, including somatostatin, arginine-vasopressin, methionine-enkephalin, cholecystokinin-8, ACTH analogue and protease inhibitor in Alzheimer's disease.

Somatostatin (SOM)

SOM shows a variety of hormonal effects on peripheral organs except brain, but the role of SOM is unclear in the neural tissues. The concentration of SOM in Alzheimer brain has been reported lower in the frontal, parietal, occipital, temporal lobe or hippocampus than in control brain. Morphological changes in SOM-immunoreactive cells were also present in Alzheimer's disease. Many SOM-positive fibers were often observed within senile plaques. The