One of the most important fields in neuroendocrinology is the study on the control of endocrine function by the central nervous system, in particular, the hypothalamic control of pituitary function. In the past decade, a great progress has been made in this field by the discovery of hypothalamic hypophysiotropic hormones. This article deals with some physiological and clinical aspects of the hypothalamo-pituitary system.

1. Function of the hypothalamus

Hypothalamic functions can be classified into 3 categories; 1) control of endocrine functions, 2) control of vegetative functions and 3) regulation of consciousness, sleep and emotion.

1) Control of the anterior pituitary function

The hypothalamus controls secretion of anterior pituitary hormones by hypothalamic releasing factors which are secreted into and transported by the pituitary portal vessels. Among the releasing factors, thyrotropin-releasing factor (TRH), luteinizing hormone-releasing factor (LHRH), somatostatin and corticotropin-releasing factor have been identified. These releasing factors are not precisely specific in their action; TRH stimulates secretion of LH and FSH and somatostatin inhibits secretion of GH and TSH. Besides these releasing factors, dopamine is known to inhibit prolactin secretion acting directly on the pituitary gland in man and animals. In addition, high concentration of dopamine is found in blood of the pituitary portal vessels. It appears, therefore, that dopamine is a major, though not a sole, prolactin-inhibiting factor (PIF). There may be other PIFs and GABA is one of the candidates.

We have observed that vasoactive intestinal polypeptide (VIP) stimulates secretion of prolactin in vivo both in man and in rats. Perfusion of dispersed rat pituitary cells in vitro has demonstrated that VIP stimulates prolactin secretion dose-dependently. In addition, we have found that VIP exists in high concentration in the pituitary portal vessels and increases by the administration of 5-hydroxytryptophan. These results strongly suggest that VIP is another prolactin releasing factor. Thus, secretion of prolactin is controlled by a complicated mechanism consisting of multiple releasing and inhibiting factors.

TRH, LHRH and somatostatin are present not only in the hypothalamus but in other parts of the brain. They have a variety of central nervous system actions and are considered to be either neurotransmitters or neuromodulators. There are many peptides in the brain which are also considered to be putative neurotransmitters. These neuropeptides affect pituitary hormone secretion when administered intravenously or intracerebroventricularly. Among the peptides, the role of opioid peptides seems to be of physiological significance, since naloxone, a specific opiate antagonist, enhances secretion of LH, FSH, TSH and ACTH. The site of action of opioid peptides seems in the brain, because they have little direct effect on the pituitary gland. Secretion of anterior pituitary hormones are also influenced by a variety of monoaminergic agents. Most of these agents affect pituitary hormone secretion by acting in the hypothalamus. It appears, therefore, that a variety of neuropeptides, monoamines and possibly amino acids act as neurotransmitters or neuromodulators that directly or indirectly influence the release of releasing factors.

2) Control of other hypothalamic function

Posterior pituitary hormones, such as vasopressin, oxytocin and neurophysins, are produced in the supraoptic and paraventricular nuclei, transported to the posterior pituitary and secreted into blood. Some neurons end at the median
eminence and vasopressin is released into the portal vessels. Therefore, permanent diabetes insipidus occurs only by the hypothalamic lesion.

The hypothalamus is involved in drinking behavior. An increased plasma osmotic pressure and hypovolemia evoke drinking behavior, and angiotensin II is known to be an important mediator. Feeding is also regulated by the hypothalamus; the destruction of the ventromedial nuclei results in hyperphagia and obesity, whereas that of the lateral hypothalamic area causes aphagia and emaciation. The hypothalamus also influences consciousness, sleep-wake cycle, circadian rhythm, emotion and memory.

2. Organic diseases of the hypothalamus

Many diseases can damage the hypothalamus, causing endocrine and non-endocrine manifestations. These symptoms are called hypothalamic syndromes. Table 1 shows causes of hypothalamic diseases seen by us since 1970. The most frequent causes of hypothalamic lesions are neoplasms: among them, craniopharyngioma is the most common, followed by germinoma and gliomas. Germinoma has features of "two-cell pattern" and is considered to be of germ-cell origin. It arises from the suprasellar region (the base of the third ventricle), the pineal region or the lateral ventricle, infiltrating extensively in the nervous tissue. The incidence of germinoma in Japan is 2.1% among brain tumors, far higher than in western countries. Non-neoplastic diseases of the hypothalamus are less common than neoplasms and comprise histiocytosis X, sarcoidosis, other types of granuloma, meningitis, encephalitis, trauma, surgery and vascular lesions. Idiopathic hypothalamic lesions are common in pituitary dwarfism, isolated pituitary hormone deficiency and diabetes insipidus.

1) Multiple pituitary hormone deficiency

Deficiency of multiple pituitary hormones is the most important endocrine manifestation in organic hypothalamic diseases. Table 2 shows symptoms associated with germinoma and craniopharyngioma in our series. Hypopituitarism, especially multiple hormone deficiency, was seen in most of the patients with supresellar germinoma and, although a little less common, in patients with craniopharyngioma. Multiple hormone deficiency was also the most common symptom in other organic lesions. In these organic hypothalamic lesions, GH deficiency was the highest in incidence, followed by gonadotropin deficiency. The incidence of decreased TSH and ACTH secretion was lower. This order in hormone deficiency was similar in Sheehan's syndrome, a typical pituitary disease.

Although clinical manifestations of hypothalamic hypopituitarism are not significantly different from those of hypopituitarism due to pituitary diseases, there are some differences in endocrinological examinations. In our studies, Sheehan's
syndrome associated with hypothyroidism showed limited response of plasma TSH to intravenous injection of TRH, whereas most of patients with suprasellar germinoma associated with hypothyroidism exhibited exaggerated and/or delayed response. Plasma LH and FSH responses to LHRH were low in almost all patients with Sheehan's syndrome and suprasellar germinoma. However, the standard LHRH test performed after 7 days' treatment with intravenous infusion of 400 µg of LHRH given over a period of 2 hours revealed almost normal response in suprasellar germinoma, but still limited response in Sheehan's syndrome. Plasma prolactin levels were low in Sheehan's syndrome but elevated in nearly a half of patients with hypothalamic lesions. Intravenous injection of TRH produced limited response of plasma prolactin in most of the patients with Sheehan's syndrome but either normal responses from normal basal levels or limited responses from high basal levels in patients with suprasellar germinoma. Therefore, these endocrinological examinations give clues in the differential diagnosis of hypothalamic and pituitary hypopituitarism.

2) Isolated pituitary hormone deficiency

We have had 30 patients with isolated gonadotropin deficiency: 6 familial and 24 sporadic cases. Four of 6 familial cases were products of consanguineous marriage. Only 2 patients had anosmia or hyposmia. The standard LHRH test revealed limited responses of plasma LH and FSH in most of the patients studied. However, 7 days' treatment with intravenous infusion of LHRH significantly improved or completely normalized plasma LH and FSH responses to LHRH. It is concluded, therefore, that most of patients with isolated gonadotropin deficiency have hypothalamic lesions and that decreased secretion of endogenous LHRH causes limited reserve of pituitary gonadotropin.

Pituitary dwarfism is classified into organic and idiopathic pituitary dwarism. In our series of 30 patients with idiopathic pituitary dwarfism, 4 were familial cases (2 families) and 19 had abnormalities in birth, such as breech presentation. Fourteen were considered to have multiple hormone deficiency, whereas 16 had isolated GH deficiency. It is still unknown whether hypothalamic or pituitary lesions are responsible for GH deficiency. It appears, however, that hypothalamic lesions are important in most cases, because exaggerated and/or delayed response of plasma TSH to TRH was observed in dwarf patients associated hypothyroidism and because propranolol, a beta adrenergic blocking agent that acts in the hypothalamus, slightly improved plasma GH responses to insulin-induced hypoglycemia.

Isolated ACTH deficiency is a relatively rare disorder with presenting symptoms of hypertension, hypoglycemia and emaciation. In our series of 7 patients, 2 had Hashimoto's thyroiditis, and each one case had rheumatoid arthritis and ankylosing spondylitis, suggesting autoimmunity in the pathogenesis of ACTH deficiency. Lysine vasopressin test revealed almost no responses of plasma ACTH and cortisol. Whether hypothalamic or pituitary lesions are responsible for this disorder should be clarified in future by using CRF.

We have had 4 patients with hypothalamic hypothyroidism due to possible isolated TRH deficiency. All were females with symptoms of cold intolerance and menstrual irregularity. One had history of meningoencephalitis and, another had history of head trauma, but remaining two were of idiopathic origin, Serum T₄ and rT₃ were low, but they increased after oral TRH administration. Plasma TSH responses to TRH were either normal or delayed, with normal response of serum T₃. Thyroid scintigrams were normal with the absence of anti-thyroglobulin or anti-microsomal antibodies. Secretions of pituitary hormones other than TSH were within normal limits. These results suggest isolated impairment of endogenous TRH secretion in these patients.

3) Precocious puberty

Precocious puberty is caused by a variety of hypothalamic diseases. Hamartoma is one of the causes of precocious puberty. Plasma LH and FSH responses were exaggerated or in adult normal range in our cases, and significantly decreased after surgery. Production of LHRH by the tumor is suggested as a cause of precocious puberty. In 3 patients with germinoma or teratoma, plasma LH levels were markedly elevated, whereas plasma FSH levels were very low. LHRH produced...
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no significant change in these hormones. Human chorionic gonadotropin (hCG) was detected in blood, suggesting hCG production by tumors. Another 3 patients with germinoma showed plasma LH and FSH responses to LHRH in adult normal range. In these patients, the mechanism controlling the onset of puberty might be disordered. Therefore, LHRH test provides important information for understanding the pathogenesis of precocious puberty.

4) Other hypothalamic syndromes

Diabetes insipidus was seen in 72 patients in our series; 11 were of idiopathic origin and 66 were secondary to neoplasms and other hypothalamic diseases. Suprasellar germinomas were especially important as a cause of secondary diabetes insipidus, since 97% of them had this disorder. Among these patients, 22% had hypernatremia associated with increased plasma osmolality probably caused by the impaired thirst mechanism. Syndrome of inappropriate secretion of antidiuretic hormone was found in only 4 patients in our series. Obesity was found in 31 patients and emaciation in 24 patients. Patients with germinoma tended to be emaciated, whereas obesity was more common in craniopharyngioma.

3. Functional abnormalities of the hypothalamus

There are several disorders with possible functional abnormalities of the hypothalamus, such as anorexia nervosa, psychogenic polydipsia, hypothalamic amenorrhea, hyperprolactinemia and deprivation dwarsim. Among them, anorexia nervosa is the most common disorder and we have had 87 patients since 1970. Eighty of them were typical cases, with the onset below age 25 and loss of weight exceeding -20% of the ideal body weight. These patients showed various endocrine abnormalities. Basal GH levels were elevated in some patients and their responses to insulin-induced hypoglycemia and arginine were either normal or impaired. TRH caused a paradoxical rise in plasma GH levels in most of the patients studied. Plasma LH and FSH responses to LHRH were limited in most of the patients with severe weight loss, but rather exaggerated in patients with mild weight loss. In the former patients, however, 3 to 5 days' administration of LHRH completely normalized plasma LH and FSH responses to LHRH. This suggests that decreased secretion of endogenous LHRH is a cause of decreased pituitary LH and FSH reserve in patients with severe weight loss. Intravenous infusion of naloxone, an opiate antagonist, failed to raise plasma LH. Plasma TSH responses to TRH were usually delayed. Serum T₃ levels were low and rT₃ levels were either normal or elevated, suggesting a decreased conversion of T₄ to T₃. Serum T₄ levels were within normal limits in most cases but decreased in some. In the latter patients, decreased serum concentration of thyroxine-binding protein was noted. Increased food intake and weight gain brought about improvement of endocrine abnormalities. These results suggest that at least most of the endocrine abnormalities result from decreased food intake and/or weight loss in anorexia nervosa.

4. Summary

Recent studies have identified structures of most of the hypothalamic hormones and clarified their actions. In addition, the importance of a variety of classical and peptide neurotransmitters or neuromodulators in the regulation of pituitary hormone secretion and other hypothalamic functions has been partly elucidated. These advances in the physiological aspects of the hypothalamus have greatly helped our understanding of the pathogenesis of a variety of hypothalamic syndromes.