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An Overview of the Hypothalamus: A Review of Hypothalamic–Pituitary Axis and Autoantibody Related Disorders

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Abstract

The hypothalamus is a portion of the brain that contains a number of small nuclei with a variety of functions. One of the most important functions of the hypothalamus is to link the nervous system to the endocrine system via the pituitary gland. The hypothalamus is located below the thalamus and is part of the limbic system. In the terminology of neuroanatomy, it forms the ventral part of the diencephalon. All vertebrate brains contain a hypothalamus. In humans, it is the size of an almond.

The hypothalamus is responsible for the regulation of certain metabolic processes and other activities of the autonomic nervous system. It synthesizes and secretes certain neurohormones, called releasing hormones or hypothalamic hormones, and these in turn stimulate or inhibit the secretion of hormones from the pituitary gland.

Keywords

Autoimmunity, Pituitary, Hypothalamus, Autoantibodies

Introduction

Anatomy of the Hypothalamus

The hypothalamus is located below the thalamus (a part of the brain that relays sensory information) and above the pituitary gland and brain stem. It is about the size of an almond.

Hormones of the Hypothalamus

The hypothalamus is highly involved in pituitary gland function. When it receives a signal from the nervous system, the hypothalamus secretes substances known as neurohormones that start and stop the secretion of pituitary hormones.

Primary hormones secreted by the hypothalamus include:

- **Anti-diuretic hormone (ADH):** This hormone increases water absorption into the blood by the kidneys.
- **Corticotropin-releasing hormone (CRH):** CRH sends a message to the anterior pituitary gland to stimulate the adrenal glands to release corticosteroids, which help regulate metabolism and immune response.
- **Gonadotropin-releasing hormone (GnRH)**: GnRH stimulates the anterior pituitary to release follicle stimulating hormone (FSH) and luteinizing hormone (LH), which work together to ensure normal functioning of the ovaries and testes.
- **Growth hormone-releasing hormone (GHRH)** or **growth hormone-inhibiting hormone (GHIH)** (also known as somatostain): GHRH prompts the anterior pituitary to release growth hormone (GH); GHIH has the opposite effect. In children, GH is essential to maintaining a healthy body composition. In adults, it aids healthy bone and muscle mass and affects fat distribution.
- **Oxytocin**: Oxytocin is involved in a variety of processes, such as orgasm, the ability to trust, body temperature, sleep cycles, and the release of breast milk.
- **Prolactin-releasing hormone (PRH)** or **prolactin-inhibiting hormone (PIH)** (also known as dopamine): PRH prompts the anterior pituitary to stimulate breast milk production through the production of prolactin. Conversely, PIH inhibits prolactin, and thereby, milk production.
- **Thyrotropin releasing hormone (TRH):** TRH triggers the release of thyroid stimulating hormone (TSH), which stimulates release of thyroid hormones, which regulate metabolism, energy, and growth and development.

Hypothalamic-pituitary dysfunction

Hypothalamic-pituitary dysfunction is a problem (or) condition with the region of the brain Known as the hypothalamus, which helps to control and regulate body functions of pituitary gland like Adrenal glands, ovaries, testes, thyroid gland.

Hypothalamic disease is a disorder presenting primarily in the hypothalamus, which may be caused by damage resulting from malnutrition, including anorexia and bulimia eating disorders, genetic disorders, radiation, surgery, head trauma,lesion,tumour or other physical injury to the hypothalamus.

Hypothalamus disorders

Hypopituitarism: The hypothalamus and pituitary gland are tightly integrated. Damage to the hypothalamus will impact the responsiveness and normal functioning of the pituitary. Hypothalamic disease may cause insufficient or inhibited signalling to the pituitary leading to deficiencies of one or more of the following hormones: thyroid-stimulating hormone, adrenocorticotropic hormone, beta-endorphin, luteinizing hormone, follicle-stimulating hormone, and melanocyte–stimulating hormones. Treatment for hypopituitarism involves hormone replacement therapy

Neurogenic diabetes insipidus

Neurogenic diabetes insipidus may occur due to low levels of ADH production from the hypothalamus.Insufficient levels of ADH result in increased thirst and urine output, and prolonged excessive urine excretion increases the risk of dehydration.

Tertiary hypothyroidism

The thyroid gland is an auxiliary organ to the hypothalamus-pituitary system. Thyrotropin-releasing hormone (TRH) produced by the hypothalamus signals to the pituitary to release thyroid-stimulating hormone (TSH), which then stimulates the thyroid to secrete T_4 and T_3 thyroid hormones Secondary hypothyroidism occurs when TSH secretion from the pituitary is impaired, whereas tertiary hypothyroidism is the deficiency or inhibition of TRH

Thyroid hormones are responsible for metabolic activity. Insufficient production of the thyroid hormones result in suppressed metabolic activity and weight gain. Hypothalamic disease may therefore have implications for obesity.

Developmental disorders

Growth hormone-releasing hormone (GHRH) is another releasing factor secreted by the hypothalamus. GHRH stimulates the pituitary gland to secrete growth hormone (GH), which has various effects on body growth and sexual development. Insufficient GH production may cause poor somatic growth, precocious puberty or gonadotropin deficiency, failure to initiate or complete puberty, and is often associated with rapid weight gain, low T_4, and low levels of sex hormones.

The Hypothalamic–Pituitary Axis

Two endocrine organs that cooperate to control the endocrine system of the body constitute the hypothalamic–pituitary axis. In fact, the hypothalamus controls the pituitary gland (or hypophysis), which in turn, by releasing different kinds of hormones, influences the majority of the endocrine glands in the body—such as thyroid, adrenal, and gonads—as well as regulates growth, milk production, and water balance. In addition to the control of the pituitary functions, the hypothalamus also has a number of connections with the limbic lobe as well as certain areas of the extrapyramidal motor system . Three lobes compose the pituitary gland: anterior, intermediate, and posterior. The thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), and growth hormone (GH) are produced by the anterior lobe. The posterior pituitary instead releases vasopressin (ADH) and oxytocin, both produced by the paraventricular and supraoptic hypothalamic nuclei. The main function of ADH is to peripherally regulate the water homeostasis, while oxytocin is secreted in response to stimulation of the uterus during labor and nipples from the infant. ADH is also released at the median eminence level, from which reaches the anterior pituitary where it stimulates ACTH cells, together with corticotrophin-releasing hormone (CRH) to produce ACTH

Diseases of the Hypothalamic–Pituitary Axis

The pituitary disorders include pituitary tumors, traumatic brain injury, hypopituitarism, hyperpituitarism, and diabetes insipidus. Pituitary tumors are typically not malignant but could affect the pituitary in its function; indeed they may generate compression causing headaches, vision difficulties, or other problem. Tumors could also cause the extra production of hormones, or their decrease. Traumatic brain injury (TBI) occurs when an external power hurts the brain. It may result in pituitary dysfunction, indeed, 20–50% of the patients with TBI have pituitary dysfunctions, among which the most frequent is the GH deficiency. Hypopituitarism is a condition characterized by a decrease in the normal production of one or more pituitary hormones, and, as mentioned, could be produced by pituitary tumors. With regard to the GH deficiency, it is most commonly due to pituitary adenomas and/or their treatment, even if many evidences show that also other causes are possible.

Often when the cause is unknown, it is defined idiopathic. The opposite condition is the hyperpituitarism, characterized by high levels of pituitary hormones. Elevated GH blood levels, often due to tumors of the pituitary, produces acromegaly while the increase in ACTH secretion stimulates the synthesis of cortisol by the adrenal glands and produces the Cushing's disease, caused by pituitary adenomas for the 80%.

Autoimmune Diseases

The autoimmune process occurs when in one individual, the cells, organs and/or tissues are attacked by their own antibodies (abs), hence named auto-abs. Consequently, all the diseases resulting from this effect are named autoimmune diseases that could be systemic or organ-specific. Systemic autoimmune diseases are characterized by the presence of auto-abs directed to non-specific tissue antigens (ags).

Autoimmunity and Hypothalamic–Pituitary Axis

The autoimmune inflammation of the pituitary gland is named lymphocytic hypophysitis, also defined as ‑autoimmune hypophysitis‖. It could affect anterior and posterior lobes or both (named lymphocytic adeno-hypophysitis, infundibulo-neuro-hypophysitis, or pan-hypophysitis, respectively. Autoimmune hypophysitis is a rare disease, with a low incidence on the general population, (approximately one in nine million/year), most commonly diagnosed in women during pregnancy or postpartum or in women affected by Sheehan's syndrome, characterized by pituitary gland necrosis, caused during or after the partu . Comorbidities can also be present including thyroiditis, type 1 diabetes mellitus, and Addison's disease. Its morphological features are suggestive of an autoimmune pathogenesis.

Aim of the Review

The aim of this review is to summarize the relevant studies reporting the auto-abs reacting to cells of the pituitary (APAs), hypothalamus (AHAs), or both, and reveal their possible relation with alterations of the hypothalamic–pituitary axis.

Hypothalamus and Pituitary Autoimmunity

The presence of both APAs and AHAs have been examined in patients affected by idiopathic hypopituitarism, traumatic brain injury with hypopituitarism, celiac disease, and Sheehan's syndrome with pituitary dysfunctions (Patients' sera were investigated through IF on unfixed baboon pituitary and hypothalamus. Among the 66 patients affected by idiopathic hypopituitarism, APAs were present at high titer (1:32–128) in 13 patients (19.6%) with pituitary dysfunctions including hypogonadotropic hypogonadism as well as ACTH and GH deficiencies, largely targeting the corresponding hormone cells, while exclusively AHAs were found at high titer in five patients with ACTH deficiency, mostly targeting CRH–secreting cells . When sera from 61 male boxers were analysed (44 competing and 17 retired), AHAs were detected in 13 (21.3%), and APAs in 14 (22.9%) of them; but in none of the 60 controls. When pituitary hormonal parameters were investigated, AHA-positive boxers (46.2%) had higher dysfunctions than AHA-negative (10.4%), but there was no significant association between APA positivity and hypopituitarism. Celiac children (n = 31, 6 with and 25 without growth deficiency) were analysed in parallel with 58 healthy controls.

Conclusions

The main approach used to reveal auto-abs includes IF that remains a widely used technique to reveal the precise location of the auto-ab reactivity within specific cell type/s of the hypothalamic–pituitary axis, combining low costs with simple use. However, through IF, the interpretation of results is often difficult due to the presence of positive reactivity often revealed also in sera from control subjects. In our opinion, a good approach is to study a high number of sera from control subjects (about 100) from which to get a threshold signal using dedicated software.

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