Exploring the Pituitary Gland Pathology, Anatomy, and Treatment Modalities: A Literature Review

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Abstract

This comprehensive literature review explores pituitary gland pathology, encompassing anatomy, physiology, and contemporary treatments. It starts by dissecting the gland's anatomy, emphasizing its role as a hormone regulator. The subdivisions, anterior (adenohipofisis) and posterior (neurohipofisis), are examined, detailing nerve fibers and neurotransmitters. Histologically, the anterior pituitary (adenohipofisis) is analyzed, highlighting cell types and their hormone secretions. The posterior pituitary (neurohipofisis) development from the hypothalamus and its hormones, like antidiuretic hormone (ADH) and oxytocin, are explored. Physiologically, the review underscores the regulated hormone secretion influenced by stimuli and feedback. Negative regulation in hormones like thyroid hormones and growth hormone is explored, elucidating hypothalamus-anterior pituitary interplay. The review transitions to pituitary pathologies, focusing on tumors. It classifies, epidemiologizes, and clinically presents pituitary tumors, emphasizing molecular complexities and genetic aspects of tumorigenesis. Closing with treatment modalities, it covers pharmacology, transsphenoidal and transcranial surgeries, and radiotherapies (fractioned stereotactic radiotherapy and Gamma Knife). Synthesizing anatomical, physiological, and clinical insights, this review offers a concise yet comprehensive understanding of pituitary gland pathology and contemporary treatments.

Keywords: Anatomy, Pathogenesis, Pituitary gland, Therapy.

1. Introduction

The intricate web of physiological processes within the human body is orchestrated by a myriad of glands, each with its specialized role. Among these, the pituitary gland, often referred to as the master gland, assumes a paramount position in regulating vital functions through the secretion of hormones. This literature review endeavors to unravel the complexities surrounding the pituitary gland, offering an in-depth exploration of its anatomy, physiology, pathology, and contemporary treatment modalities. The pituitary gland, situated within the sella turcica, emerges as a pivotal player in endocrine control. Its intimate connection with the hypothalamus forms the neuroendocrine axis, orchestrating the release of hormones that govern diverse bodily functions. The anterior and posterior lobes of the pituitary, each with distinct functions, intricately coordinate hormonal secretions, maintaining a delicate balance essential for homeostasis.

A cornerstone of this review lies in the detailed examination of pituitary pathology. The gland's susceptibility to tumors, particularly adenomas, is a central focus. Classifications, including prolactinomas, somatotrophs, and corticotrophs, are elucidated, shedding light on the diversity of these neoplasms (Balasubramanian et al.,

2020). The genetic landscape, encompassing mutations like GNAS and USP8, adds a molecular layer to comprehending pituitary tumorigenesis. Exploring the anatomy and physiology lays the foundation for understanding the manifestations of pituitary disorders (Hong et al., 2016). The vasculature supplying the gland, the intricacies of the hypothalamic-pituitary axis, and the role of neurotransmitters provide a holistic perspective on the gland's functionality. This sets the stage for delving into the clinical presentation of pituitary tumors, their impact on hormonal balance, and potential consequences for adjacent structures (Møller et al., 2020).

Epidemiological insights, drawn from diverse populations, enrich the understanding of pituitary disorders (Agustsson et al., 2015).Variances in tumor distribution, prevalence, and associated hormonal dysregulations are explored, offering a comprehensive view of the global landscape. Notably, the incidence of adenomas and their categorizations, including functional and non-functional types, further refines our comprehension. Contemporary treatment strategies constitute a pivotal component of this review. Pharmacological interventions, such as dopamine agonists for prolactinomas, and surgical approaches, notably the transsphenoidal method, take center stage. Advances like endoscopic surgeries and radiotherapeutic techniques, including Gamma Knife radiosurgery, highlight the ongoing evolution in managing pituitary disorders (Trifiletti et al., 2019). In essence, this literature review is crafted with the intent to synthesize multifaceted aspects of pituitary gland functioning and pathology. It seeks to bridge anatomical, physiological, and clinical dimensions, providing a holistic perspective on the intricacies of this master gland. As the landscape of endocrinology advances, this review aims to serve as a compass, guiding clinicians, researchers, and enthusiasts through the nuanced terrain of pituitary gland intricacies.

2. Review Content

2.1 Pituitary Gland

Anatomy of the Pituitary Gland

The pituitary gland, or pituitary, is a bean-sized organ located within the sella turcica. It regulates the secretion of hormones from other glands and their target organs within the body. The pituitary gland is divided into two subdivisions: the adenohypophysis (anterior pituitary) and the neurohypophysis (posterior pituitary). Nerve fibers and neurotransmitters from the hypothalamus enter the pituitary, coordinating the release of hormones produced or stored in the pituitary. Remnant cells of Rathke's pouch are retained between the adenohypophysis and neurohypophysis as vesicles containing colloid. The infundibulum is covered by an endocrine cell layer known as the pars tuberalis. Blood supply to the pituitary comes from the superior and inferior hypophyseal arteries, branches of the internal carotid artery (Gartner and Hiatt, 2011). Blood supply to the anterior and posterior pituitary originates respectively from the superior and inferior hypophyseal arteries, both branching off the internal carotid artery. Additionally, a separate portal vein system, supplied by branches of the superior hypophyseal artery, carries hormonal signals from the hypothalamus. Venous drainage primarily occurs through the anterior lobe, with venous tributaries initially flowing into the cavernous sinus, then into the petrosal sinus, and finally into the internal jugular vein (Balasubramanian, 2020).

Histology of the Pituitary Gland

Anterior Pituitary (Adenohypophysis)

The anterior pituitary, or adenohypophysis, originates from Rathke's pouch and is divided into three parts: pars distalis, pars intermedia, and pars tuberalis (Balasubramanian, 2020). The capsule of the pars distalis

sends reticular fibers into the connective tissue supporting the parenchymal cells and sinusoidal capillaries from the base of secondary capillaries. The parenchymal cells of the pars distalis consist of two types: chromophil cells with histologically stainable secretory granules, known as acidophils and basophils. Acidophils, the most abundant cells in the pars distalis, include somatotrophs that secrete somatotropin (growth hormone) and mammotrophs that secrete prolactin, a hormone promoting mammary gland development during pregnancy and lactation. Basophils are located peripherally in the pars distalis. Three subtypes include corticotrophs that secrete adrenocorticotropic hormone (ACTH) and lipotropic hormones, thyrotrophs that secrete thyrotropin, and gonadotrophs that secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Lastly, chromophobes have minimal cytoplasm, few secretory granules, and do not stain histologically. These cells may be chromophils that have released their secretory granule contents, although some researchers suggest chromophobes may be stem cells. The most prominent cells in the pars distalis are folliculostellate cells, whose function is still unknown. The pars intermedia, situated between the anterior and posterior lobes, contains cysts with colloid from Rathke's pouch and a group of basophils producing pro-opiomelanocortin. α-Melanocyte-Stimulating Hormone (α-MSH), B-Endorphin, Corticotropin, and Lipotropin are all formed by the cleavage of this prohormone. In humans, α-MSH induces prolactin release and is known as a prolactin-releasing factor. The pars tuberalis covers part of the pituitary stalk. Although not described as a hormone-secreting region, some of its cells contain FSH and LH (Balasubramanian, 2020).

Posterior Pituitary (Neurohypophysis)

The posterior pituitary, or neurohypophysis, develops from the hypothalamus and is divided into three regions: median eminence, infundibulum, and pars nervosa. The entire neurohypophysis can be considered an extension of the hypothalamus. The hypothalamo-hypophyseal tract consists of non-myelinated nerve cell axons located in two hypothalamic nuclei (Supraoptic and paraventricular). Neurosecretory cells from these nuclei produce antidiuretic hormone (ADH, vasopressin), oxytocin, and neurophysin carrier proteins that bind to these hormones. The hypothalamo-hypophyseal tract terminates in the pars nervosa, and these axons are supported by pituicytes, glia-like cells characteristic of this pituitary region. ADH and oxytocin hormones are stored in an active state in axons (Herring bodies) and are released as needed around fenestrated capillary bases formed by two inferior hypophyseal arteries (Gartner and Hiatt, 2011).

Physiology of the Pituitary Gland

The anterior pituitary consists of five distinct cell types, each secreting different hormones. Each cell type originates from the same progenitor cell in response to the expression of specific transcription factors; deficiency in these transcription factors results in genetic hypopituitarism syndromes due to the lack of specific anterior pituitary cell types (Pfäffle and Klammt, 2011). The secretion of hormones from the anterior pituitary is a tightly regulated process influenced by physiological stimuli and feedback control from effector organs. Generally, the release of hormones from the hypothalamus travels to the pituitary gland through the portal circulation. These releasing hormones trigger the release of anterior pituitary hormones, which then act on their target organs to produce biological effects (Hong et al., 2016).

Negative regulation of most anterior pituitary hormones occurs through feedback from target organ hormones on the hypothalamus and/or anterior pituitary. Negative control of thyroid hormones (free T4, FT4), cortisol, growth hormone (GH), and reproductive hormones is achieved through this paradigm. It's worth noting that the negative regulation of GH is also mediated by somatostatin, a hormone that increases in response to GH and IGF-1. This physiology has been exploited through the use of synthetic somatostatin analogs to treat GH-producing tumors (Gadelha et al., 2013). Prolactin regulation differs from other anterior pituitary hormones because prolactin secretion is tonically inhibited by dopamine from hypothalamic neurons. Physiological triggers of prolactin secretion (sleep, stress, breastfeeding, pregnancy) decrease dopamine secretion from the

hypothalamus, allowing lactotrophs to release prolactin. Pharmacological blockade of dopamine receptors on lactotrophs (e.g., by antipsychotics) also leads to increased prolactin secretion (Hong et al., 2016).

2.2 Pituitary Tumors

A pituitary tumor is an abnormal enlargement of the pituitary gland that is generally a slow-growing tumor. Although most are asymptomatic, pituitary tumors can cause symptoms depending on hormonal activity. Even non-functioning pituitary tumors can cause symptoms due to their intracranial mass effects (Gittleman et al., 2014). Pituitary tumors are divided into pituitary adenomas and pituitary carcinomas. Pituitary adenomas are benign neoplasms in the anterior pituitary that can disrupt hormonal regulation in affected individuals. Pituitary adenomas are the most common type of pituitary tumor and the most frequently encountered intracranial tumor (Saeger et al., 2007). Based on size, pituitary adenomas are classified into microadenomas if the tumor diameter is <10 mm and macroadenomas if the tumor diameter is >10 mm (Lake, 2013). Based on hormonal regulation disturbances, pituitary adenomas are further classified into functional and non-functional. Functional pituitary adenomas secrete various hormones and are divided into prolactin-secreting adenomas (prolactinomas) (about 40%), growth hormone-secreting adenomas (about 11-13%), adrenocorticotropic hormone (ACTH)-secreting adenomas (about 1-2%), thyrotropin (TSH)-secreting adenomas (<1%), and very rarely gonadotropin-releasing hormone (GnRH)-producing adenomas (Lake, 2013). Pituitary carcinomas can only be diagnosed if there is cerebrospinal and/or systemic metastasis. These carcinomas can develop through the transformation of adenomas or de novo from non-tumor adrenohypophysis cells. Pituitary carcinomas more commonly produce PRL or ACTH (Heaney, 2011). The distribution of tumors varies in different population-based studies. According to a study in Iceland from 1955 to 2012, 471 patients were identified with non-functional pituitary tumors (43.0%) as the most common pituitary tumor, followed by prolactinomas (39.9%) (Agustsson et al., 2015).

Pathology and Pathogenesis

The differentiation of pituitary cell lineages expressing hormones can lead to adenomas, often associated with autonomous hormone hypersecretion. Different hypersecretion syndromes depend on the cell of origin: corticotroph adenomas secreting corticotropin cause Cushing's disease, somatotroph adenomas secreting growth hormone cause acromegaly, lactotroph adenomas secreting prolactin cause hyperprolactinemia, and thyrotroph adenomas secreting thyrotropin cause thyrotoxicosis. Gonadotroph adenomas, usually non-secreting, lead to hypogonadism and often manifest as an incidental sellar mass. Permissive hypothalamic hormones and paracrine proliferative signals result in irregular pituitary cell cycles, with aneuploidy, variations in chromosome copy numbers, and cellular aging resisting malignant transformation. Although mutations in GNAS (gene for alpha subunit of guanine nucleotide-binding protein [G-protein] stimulating adenylate cyclase) and USP8 (gene for ubiquitin carboxyl terminal hydrolase 8, a specific ubiquitin protease) occur in a subset of nonfamilial growth hormone-secreting tumors and corticotropin-secreting tumors, genetic evaluation of sporadic adenomas rarely aids management (Melmed, 2020). Pituitary adenomas arise from differentiated hormone-expressing cells or from null cells. The clinical phenotype is determined by the cell of origin and the presence or absence of autonomous and specific hormone hypersecretion. Prevalence data are estimates. IGF-1 indicates growth factor receptor insulin 1, SF1 indicates steroidogenic factor 1, and Tpit indicates T-box factor Tpit, pituitary (Melmed, 2020).

Pathophysiology

Significant progress has been made in characterizing the molecular basis of pituitary tumorigenesis; however, current evidence does not point to any of these changes as a 'primary' event responsible for sporadic tumors. Mutations in recognized tumor suppressor genes and oncogenes seem not to play a crucial role in most pituitary adenomas. However, methylation-mediated or associated gene silencing, particularly of tumor

suppressor genes, has been reported by many researchers. Several genes (e.g., PTTG, Pdt-FGFR4, GADD45G, MEG3A, ZAC, DAP kinase, PTAG, and p27) have been involved in pituitary tumorigenesis. PTTG (securin) appears associated with invasiveness and aggressiveness of pituitary adenomas. Cellular signaling abnormalities have been identified in pituitary tumors, but their genetic basis is unknown. Both the PI3K/Akt/mTOR and Raf/MEK/ERK pathways are overexpressed and/or overly active in many pituitary tumors, resulting in the inhibition of cell cycle inhibitors, as seen in the β-catenin and HIF pathways. These pathways may share a common root at various stages, including activation of early receptor tyrosine kinase pathways and interactions with downstream regulators, including c-myc or cyclin D1. For most pituitary tumors, molecular defects remain unexplained, and more vulnerability genes may be identified. Modern genetic, genomic, and molecular biology approaches are expected to reveal new mechanisms of endocrine tumorigenesis aimed at developing better diagnostic, prognostic, and therapeutic tools (Dworakowska and Grossman, 2009).

2.3 Treatment

For prolactinomas, dopamine agonist therapy can be performed to reduce prolactin levels, decrease tumor size, and restore gonadal function for patients with symptomatic microadenomas or macroadenomas secreting prolactin (Melmed et al., 2011). In surgery, the transsphenoidal approach can be effectively used for 95% of pituitary tumors. Exceptions include large tumors with significant anterior extension into the temporal cranial fossa, which may require a transcranial approach. Occasionally, a combined transsphenoidal and transcranial approach can be used. However, some surgeons prefer to extend the transsphenoidal exposure base to remove these tumors and avoid craniotomy (Kaptain et al., 2001). There are two types of transsphenoidal approaches, the microscopic approach was the gold standard for pituitary adenoma surgery before 1992. This approach has been refined to reduce tumor signs and symptoms and minimize postoperative complications (Møller et al., 2020). Besides, endoscopic transsphenoidal surgery offers the advantage of better tumor visualization, especially for laterally invasive or large tumors. Improved visibility allows for more effective tumor removal, resulting in reduced signs and symptoms. However, this advantage may pose a higher risk of cerebrospinal fluid (CSF) leakage (Broersen et al., 2019). Beside that, craniotomy has traditionally been used to access intracranial tumors in various locations. Craniotomy is an approach for tumors with broad cranial base extension. In these cases, craniotomy is a more effective operation with better access to the tumor. Moreover, craniotomy is a safe procedure for neurovascular tissue around clear and extensive dissection areas. Craniotomy is highly effective for managing giant pituitary macroadenomas or orbitofrontal meningiomas (Musleh et al., 2006). Fractionated Stereotactic Radiotherapy (FSRT) is performed for patients with brain metastases. FSRT is administered to patients with a tumor maximum dimension $\geq$ 3cm and a distance between the tumor and the optic apparatus $\leq$ 5 mm (Puataweepong et al., 2015). The goal of radiosurgery, including all radiosurgery techniques, is to deliver a high dose of radiation to the tumor while minimizing the dose to adjacent critical structures such as the optic structures, hypothalamus, medial temporal lobe, and brainstem. Gamma Knife is a well-validated and modern radiosurgery platform that allows for precise management of pituitary tumors (Trifiletti et al., 2019).

3. Conclusion

In conclusion, this review highlights the intricate interplay between the hypothalamus and anterior pituitary in hormone regulation. It delves into the complexities of pituitary tumors, emphasizing their classifications, epidemiology, and molecular underpinnings. The multidimensional approach to treatment, encompassing pharmacology, surgery, and radiotherapy, underscores the evolving strategies in managing pituitary disorders. Overall, the synthesis of anatomical, physiological, and clinical insights provides a nuanced understanding of pituitary gland pathology, guiding contemporary treatment approaches.

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