A FUNCTIONAL TREATMENT FOR A NON-FUNCTIONING ADENOMA

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Introduction

Editorial

Here is a riddle for you: it is a regulator of many physiological processes; it determines growth, temperature, blood pressure; it dictates whether you feel stressed or sleepy, or if you need to pee; it decides if you become fat or not, by controlling your energy metabolism. Have you guessed it yet? It is situated in the brain, the size of a pea and has no real autonomy, but is merely an executant, subject to higher control mechanisms. Yet, complications can arise with the dysfunctioning or absence of this tiny gland. The pituitary gland, sometimes also known as the hypophysis, is with its function of an endocrine gland, responsible for the production and secretion of hormones that influences other endocrine organs and many processes in your body.

The pituitary gland, situated in a small bone cavity called sella turcica outside the blood-brain-barrier, is broadly distinguishable into two lobes that have a different embryological origin. The anterior pituitary or adenohypophysis, formed from Rathke's pouch. The second lobe is the posterior pituitary, also called the neurohypophysis, which is neural tissue outgrowth from the hypothalamus (see figure 1). The different origins of the pituitary gland are still visible today, both anatomically and functionally. The anterior pituitary consists of endocrine cells that are also able to produce hormones. The posterior pituitary is continuous with the hypothalamus and consists of nerve endings in which hormones that are produced by the hypothalamus are stored. This means that the neurohypophysis is directly and anatomically connected to the hypothalamus, but the adenohypophysis is not. Still, the adenohypophysis receives input and is thus regulated by the hypothalamus. Neurons in the hypothalamus secrete neurohormones, like somatostatin, that reach the anterior pituitary via the hypophyseal portal vessels and stimulate or inhibit hormone production and secretion [1-3].

The anterior pituitary

The adenohypophysis takes up approximately two thirds of the pituitary gland and can produce and secrete a wide range of hormones with diverse functions. One of the six most important hormones that is produced and secreted by the anterior pituitary is the growth hormone (GH), also known as somatotropin. About 50% of the cells in the adenohypophysis are somatotrophs and synthesise this hormone. GH exerts its influence all over the body and is the only major anterior pituitary hormone that does not stimulate target glands. Instead, it stimulates protein synthesis and overall growth of cells in virtually all tissues by promoting an increase in cell size and mitosis. GH release is controlled by growth hormone releasing hormone and growth hormone inhibitory hormone (somatostatin), released by the hypothalamus. The effects are not immediate; it can take months for GH to become effective. About 15-20% of other cells that occupy the adenohypophysis are corticotropes. Upon stimulation by hormones from the hypothalamus, these cells produce and secrete adrenocorticotropic hormone (ACTH, also called corticotropin). This hormone stimulates the adrenal cortex to produce glucocorticoids, like cortisol, and androgens, which have regulative functions for the metabolism of proteins, carbohydrates and fats. Another 10-25% of the cells in the adenohypophysis are lactotropes, synthesising prolactin. The release of prolactin is inhibited by prolactin-inhibiting hormone, more commonly known as dopamine. Its best known function is influencing the mammary glands to stimulate milk production and secretion. Gonadotropes produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and occupy about 10-15% of the anterior pituitary. LH and FSH are important for controlling gamete and sex hormone production. They stimulate, amongst others, testosterone production and ovulation, and they regulate spermatogenesis. The release of LH and FSH is promoted by gonadotropin-releasing hormone from the hypothalamus. Finally, thyrotropin-releasing hormone from the hypothalamus stimulates the release of thyroid-stimulating hormone (TSH) by thyrotrope cells. TSH stimulates the synthesis and secretion of hormones produced by the thyroid gland, namely T3 and T4, which in turn affect the body metabolic rate. Thyrotropes fill 3-5% of the adenohypophysis [1-3].

The posterior pituitary

Contrary to the adenohypophysis, the neurohypophysis does not produce hormones, but secretes them. Two known hormones are vasopressin, also known as antidiuretic hormone (ADH), and oxytocin. The nerve endings in the posterior lobe originate in certain nuclei of the hypothalamus, from which the hormones are transported to the pituitary gland. It may take several days before hormones produced in the cell bodies of the nuclei finally reach the posterior pituitary. Vasopressin is primarily synthesised in the supraoptic nuclei and serves to maintain blood osmolality and blood pressure. A slight increase in osmolality causes rapid secretion of vasopressin into the circulation, where it directly affects the re-

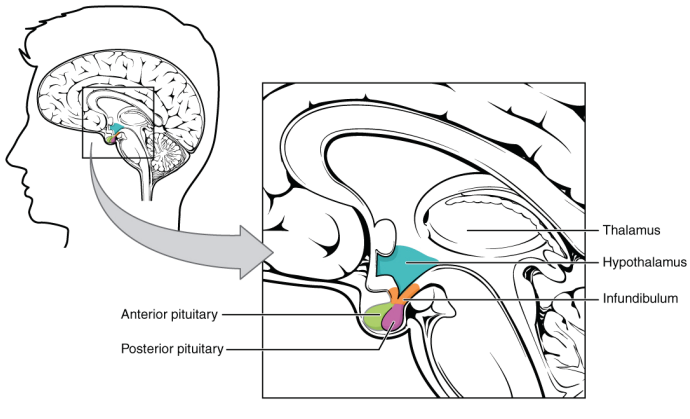

Figure 1: *Anatomy of pituary gland. OpenStax College. Anatomy & Physiology, Connexions Web site. Jun 19, 2013. http://cnx.org/content/col11496/1.6/*

absorption of water in the kidneys, more accurately, the collecting duct. There, vasopressin increases the permeability of the renal cell membranes by mobilising aquaporins: water permeable pores. This prompts the retention of water and decreases osmolality. The other function of vasopressin, maintaining blood pressure, works via the same mechanism, but is initiated by low blood pressure or blood volume. Furthermore, higher concentrations of vasopressin can induce vasoconstriction to increase blood pressure. Oxytocin is primarily produced in the paraventricular nuclei and is often called the "cuddle" or "love" hormone for its importance in social and emotional bonding between beings, and finding trust and intimacy. Moreover, this hormone is important for lactation in breastfeeding women and can induce contraction of the uterine muscles during labour. Oxytocin can be administered with the purpose of inducing labour in pregnant women [1-3].

Relevance of the pituitary gland

Both lobes serve the crucial function of secreting hormones and receive input from the hypothalamus, giving the pituitary gland barely any autonomy. Does this make the pituitary gland redundant? Can its functions not just be taken over by the hypothalamus? Are the extra steps with the stimulatory or inhibitory 'messenger' hormones needless and just causing another possibility for complications? The answer is simple: no. The role of the pituitary gland as described above is not as clear-cut and straightforward as may have been depicted; it involves many complicated pathways and processes. Although this gland is an intermediate between the hypothalamus and peripheral organs and its hormone secretion is mainly regulated by the hypothalamus, the latter is not the sole dictator of pituitary outputs. Research has shown that the regulation of the pituitary gland's function is also dependent on local interactions between pituitary cells. In the adenohypophysis, cells of the same cell type that produce the same hormones are called cell clusters. Cellular communication between the cells in the same cell clusters is important for the simultaneous activation of these cells. Upon activation of one of the cells in the cluster, second messengers can travel to the other cells via i.a. gap junctions. This way, cells in the same cluster are connected to each other, so that hypothalamic hormones can activate all cells in these clusters at once. Also communication between pituitary cells that secrete different hormones is important. This can be managed through soluble factors. Thus, the pituitary gland also regulates its own function and is not only controlled by the hypothalamus [4].

Pituitary adenomas

All these complicated processes can be disturbed, leading to a variation of diseases. One of these is a pituitary gland adenoma, which can either be a 'functioning' tumour, which secretes pituitary hormones, or a non-functioning tumour, which does not produce pituitary hormones. Functioning tumours secrete hormones like ACTH, GH, prolactin or TSH. This can result in disorders like Cushing's disease, gigantism, hyperprolactinemia or hyperthyroidism. Here, we will focus on the non-functioning pituitary adenomas (NFPAs) and their development, symptoms and possible treatments.

Pathogenesis

Most pituitary adenomas, especially NFPAs, are sporadic and often detected by accident. Usually, tumours evolve due to the manifestation of oncogenes like RAS and the inactivation of tumour suppressor genes such as P53, but in the development of a pituitary adenoma mutations in such genes rarely play a role. Although some genes that give an individual a predisposition to pituitary neoplasms have been identified, like GNAS and MEN1, they are mostly not involved in the pathogenesis of sporadic pituitary tumours [5]. Pituitary adenomas are often monoclonal in origin, meaning that all tumour cells are derived from a single, abnormal pituitary cell. The gene expression can be altered by epigenetic modifications, and it has been shown that this is frequently the cause for a different expression of genes in pituitary adenomas. One of the genes that is often epigenetically modified in both functioning tumours and NFPAs is the pituitary tumour transforming gene (PTTG), which is usually highly expressed in pituitary tumour cells. PTTG acts as a controller of the separation of sister chromatids during metaphase and is a proto-oncogene that facilitates cell cycle progression [6]. Because PTTG inhibits the separation of the sister chromatids by inhibiting the activity of separase in anaphase, they are pulled to the same pole. This results in aneuploid daughter cells and chromosomal instability [7]. All in all, the pathogenesis of pituitary adenomas is complicated and not completely understood.

Treatments

There are a couple of options to treat NFPAs, like surgical resection, radiation therapy, medical management or observation. Surgical intervention has been the preferred method of treatment in symptomatic patients because the refinement of surgical approaches to the sella turcica has been improved.

The outcome of surgical intervention has been very positive. It results in an immediate tumour volume reduction of up to 64%-90% in nearly all patients and both visual function and hypopituitarism improve. But, as with every treatment, complications can occur. Halvorsen et al. [8] demonstrated the complication rate of surgical intervention. They describe a total complication rate of 7.1%. These complications include cerebrospinal fluid (CSF) leak, meningitis and visual deterioration.

Despite these side effects, surgical intervention seems to be the best treatment for NFPAs. The second best options for the treatment of NFPAs are radiation therapy and radiosurgery. The effects of mono-radiation therapy are minor compared to the effects achieved by surgical resection, and risk of tumour progression and radiation-induced hypopituitarism are major barriers for radiation monotherapy. An example for radiosurgery is gamma knife radiosurgery, which differs from traditional surgery because there is no incision. The gamma knife technique uses 200 tiny beams of radiation with submillimetre accuracy [17]. Studies about the effect of gamma knife radiosurgery revealed that not all patients showed a reduction of the tumour and some even showed a progression in tumour size [9, 10].

Another option of the treatment of NFPA is medical therapy. Unfortunately, this has not been proven effective in the primary management of NFPA. Dopamine agonist and somatostatin analogs are useful medicine in the treatment of hormone producing pituitary adenoma. Unfortunately, these medications haven't shown a significant therapeutic effect on the adenomas [11]. Thus, surgical resection remains the preferred method for treating NFPA.

Surgical possibilities

Pituitary adenomas are usually removed through a transsphenoidal approach, during which an endoscope is or instruments are inserted through the nose and the sphenoid bone. However, larger adenomas are best operated with a transcranial approach, where the brain is exposed through the skull, or a combined approach that include both approaches [12]. Han et al. confirmed that the transsphenoidal and transcranial approaches for giant pituitary adenomas (diameter >4 cm) should be combined flexibly based on the characteristics of the tumour. In certain cases, this simultaneous combined approach maximizes the tumour extirpation and lowers the risk of swelling and bleeding of the residual tumour [13]. The transsphenoidal route has not always been the preferred operation technique, because the space the surgeon has to work in is very narrow which makes it very difficult to perform. However, since

the availability of more sophisticated endoscopes that provide a more optimal angle of view, the transsphenoidal approach is less invasive and more effective than it has ever been.

Besides the endoscopes, more technological adjuncts are used during transsphenoidal surgery for NFPAs. Both endoscopes and operative microscopes can be used for the visualization during NFPA surgery. Other technological adjuncts are neuronavigation, intraoperative magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) diversion, and dural closure techniques. Neuronavigation uses a computer program in which an image of the brain of the patient is imported. A tracking system very similar to a GPS-system gives the surgeon insight into which part of the brain his instruments are located at that moment. Intraoperative MRI improves the rate of gross total tumour resection but is not recommended, since it results in an increased false-positives rate. CSF diversion, used as treatment for hydrocephalus, is a procedure that is used to drain fluid from the brain and spinal cord, usually to the abdomen. Perioperative CSF diversion might prevent postoperative CSF leak. Unfortunately, there is still insufficient evidence for the use of neuronavigation, CSF diversion or dural closure techniques [14]. More research is needed to determine whether these techniques can be used to optimise the transsphenoidal surgery.

The endoscopic or microscopic transsphenoidal surgery is the preferred treatment for symptoms by NFPA. However, not all patients are suitable for this technique.

Operation indications

Not every patient with NFPA has an indication for surgery. Visual disorders, pituitary deficiency and headaches are symptoms that are an indication for surgery. Of course, the doctor must be sure that nothing else is causing these symptoms. Especially for headaches a surgery might not help, because there's not always a direct causal relation between a headache and an adenoma.

Messerer et al. recommend surgery at the asymptomatic stage of macroadenoma, because of the improved endocrinological and visual outcome [15]. Currently, some patients with asymptomatic adenoma have an indication for surgery. Whether a patient without symptoms gets an indication for operation depends on several factors: patient age, natural course of non-functioning adenoma, the risk of onset of visual disorders, risk of onset of pituitary deficiency and risks inherent to the surgery. Young patients will be more likely to get an indication for non-emergency surgery, because of the almost inevitable progression of adenoma over the long term and lower risks inherent to surgery. Like every patient, each NFPA is different. They are subdivided into macroadenoma and microadenoma. These two subdivisions differs in the progression, the progression is slower in microadenoma in comparison with macroadenoma. Microadenoma is almost never an indication for surgery: it is unlikely that the tumour progresses. Due to the slow tumour growth, problems will not occur during a person's life.. However, macroadenoma may indicate non-emergency surgery, based on its natural progression. An NFPA is almost always a macroadenoma [16].

Conclusion

Because there are no medicines available for NFPA, surgery is the preferred treatment for NFPAs. There are a few options to operate, but transsphenoidal surgery seems to be the best choice. This technique immediately reduces tumour volume and it is less invasive in comparison with transcranial surgery. However, as with every operation, there are risks attached. Therefore, it's necessary to only select the patients who are really in need of such an operation. When a patient shows symptoms, the time is right to operate. But the decision to operate or not becomes more complex when a patient doesn't show any symptoms. More evidence is needed to determine whether a patient without symptoms benefits more from a preventive operation.

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