Hypopituitarism : clinical assessment in different conditions
Kokshoorn, N.E.

Chapter 1

General introduction and outline of this thesis

Contents

I.   General introduction

The pituitary gland is the master regulator of the endocrine system. Different pathophysiological conditions can affect the function of the pituitary gland and, consequently, endocrine homeostasis. The evaluation of pituitary function is therefore complex and the different tools that have become available to evaluate pituitary function only provide limited information of different aspects of hormone secretion. In this thesis, several difficulties encountered in establishing a diagnosis of pituitary insufficiency are studied in different pathophysiological conditions.
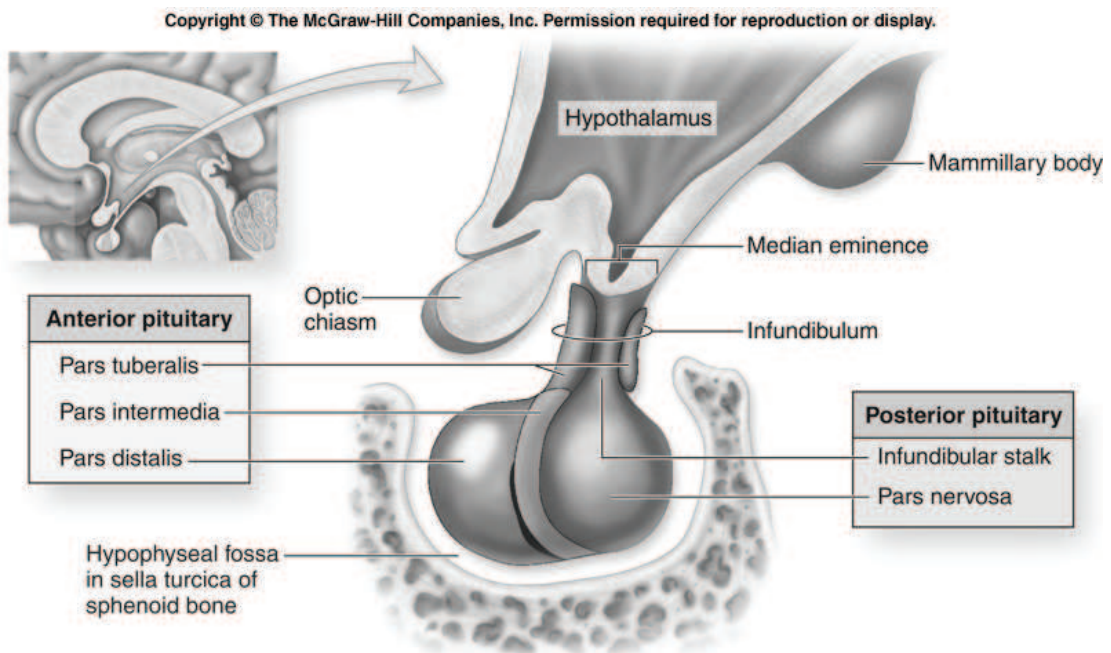
Figure 1. The pituitary gland

II. The pituitary gland

Anatomy and Physiology

The pituitary gland is a small gland located at the base of the skull in a socket of sphenoid bone, called the sella turcica. The gland consists of two lobes, the anterior lobe (or adenohypophysis; 80%), and a posterior lobe (neurohypophysis; 20%) (Figure 1).

Together with the hypothalamus, the pituitary controls the function of different endocrine glands (*i.e.* thyroid, adrenal and reproductive glands) (1). The hypothalamus receives signals from upper corticol inputs and the environment (such as light and temperature) and, in turn, delivers signals to the pituitary gland (*i.e.* regulating the endocrine system). Hormones released by the pituitary gland influence the endocrine systems in the body and also have a feedback on the hypothalamus.

The communication between the hypothalamus and anterior pituitary is via the portal system that runs through the pituitary stalk. Hormones released by the hypothalamus are delivered to the anterior pituitary through these vessels and reach the anterior lobe through a dense capillary network. The communication with the posterior gland is via axons and nerve terminals of larger neurons that originate from within the hypothalamus. The hormones produced in these neurons, arginine-vasopressin and oxytocin, are released directly from the posterior pituitary into the systemic circulation.

The anterior pituitary is controlled by specific hypothalamic hormones: thyrotropin releasing hormone (TRH), gonadotropin releasing hormone (GnRH), corticotropin releasing hormone (CRH), growth hormone releasing hormone (GHRH), and somatostatin, that bind specific transmembrane receptors expressed in different anterior pituitary cells. These anterior pituitary cells are classified by their specific secretory products: somatotrophs (GH-secreting cells, expressing the GHRH and somatostatin receptor; 50%), lactotrophs (PRL-secreting cells, expressing the prolactin receptor; 10–25%), corticotrophs (cells secreting ACTH,

expressing the CRH receptor; 15–20%), thyrotrophs (cells secreting TSH, expressing the TRH receptor; 10%), and gonadotrophs (LH and FSH secreting cells, expressing the GnRH receptor; 10–15%) (2).

## 1. Regulation and secretion of growth hormone and IGF-I

The regulation of growth hormone (GH) secretion is complex and involves many stimulatory and inhibitory hypothalamic peptides. However, the two most important components are growth hormone-releasing hormone (GHRH), which stimulates the somatotrophic cells, and somatostatin (SST) which inhibits GH release (2). The secretion of GH is also affected by factors such as nutrition (increased in fasting, stimulated by high protein meals and inhibit by hyperglycemia and leptin), other hormones (stimulated by estrogens and inhibited by glucocorticoid excess), neuropeptides, neurotransmitters and opiates (2–4).

The secretion of GH is pulsatile with undetectable serum GH levels between the pulses. In normal subjects the 24-hour profile of plasma GH levels consists of stable low levels interrupted by bursts of secretion (Figure 2 and 3). The major determinant of GH secretion in humans is sleep. GH secretion is lower in elderly and obese subjects and there are sex-specific differences in GH pulse amplitude and mass (5;6). The age-associated changes in the GH profile include a reduction in GH secretory burst frequency, the half life of endogenous GH and the daily secretory rate (7). In obese subjects decreased GH concentrations result from both diminished pulsatile GH secretion and accelerated metabolic clearance (4;8).

In the liver, GH stimulates the production of insulin-like growth factor (IGF-I). The primary function of GH is promotion of linear growth in children by acting directly and indirectly (via the synthesis of IGF-I which mediates most of the peripheral actions of GH) on the epiphyseal plates of long bones. Whereas GH and IGF-I have synergistic effects on linear and organ growth by their control of mitogenesis and apoptosis and on glomerular filtration rate, their metabolic actions are opposing: GH stimulates lipolysis and reduces insulin sensitivity, IGF-I is anti-lipolytic and ameliorates insulin sensitivity (9;10).
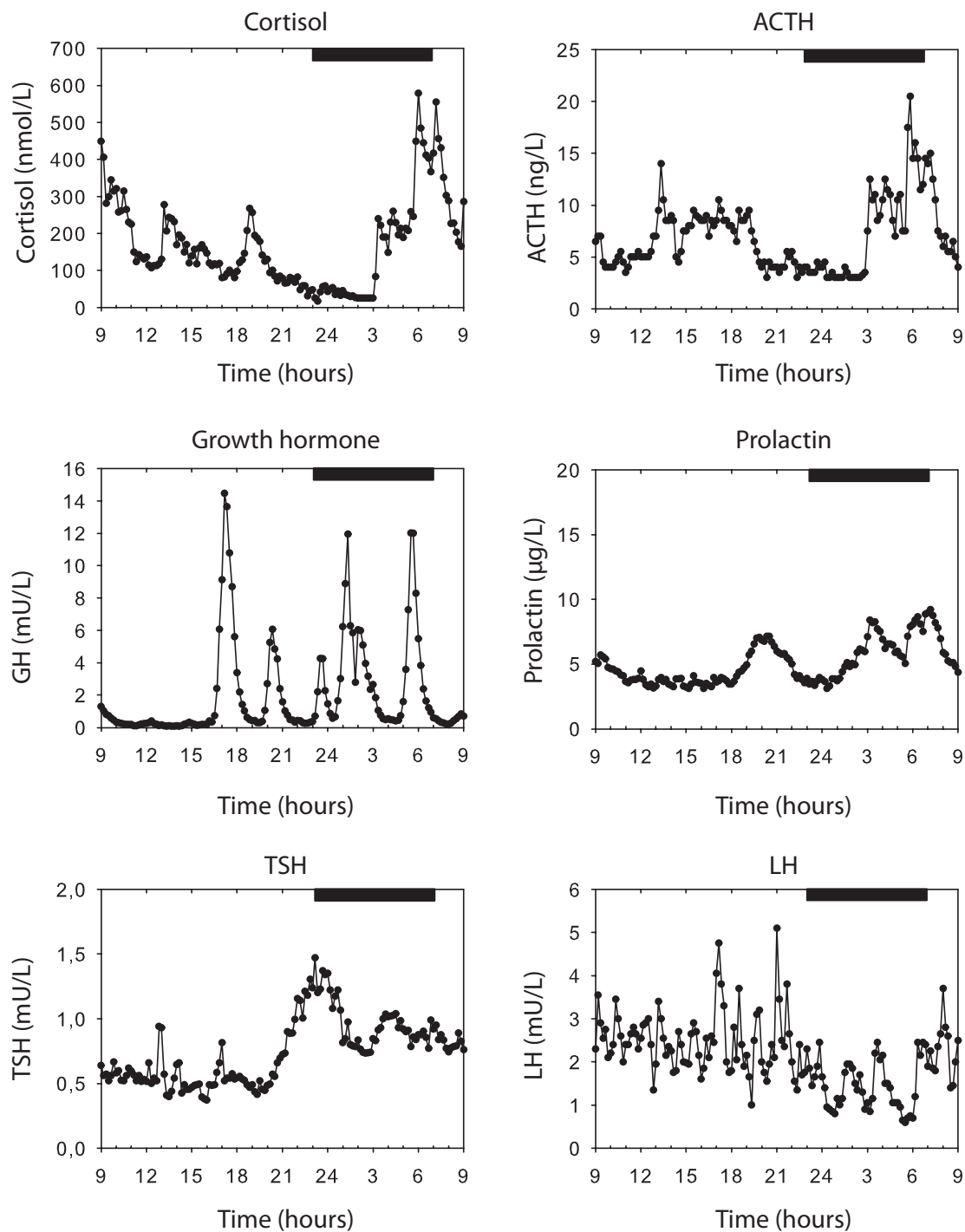
Figure 2. Plasma hormone concentration profiles of a 33 year-old healthy female volunteer. Blood samples were taken at 10 min intervals during 24 hours. The black bar in the top of the panels indicate the period with lights off. Note the diurnal and the pulsatile characteristics of each hormone. *(The figure was provided by Dr. F. Roelfsema, Leiden University.)*

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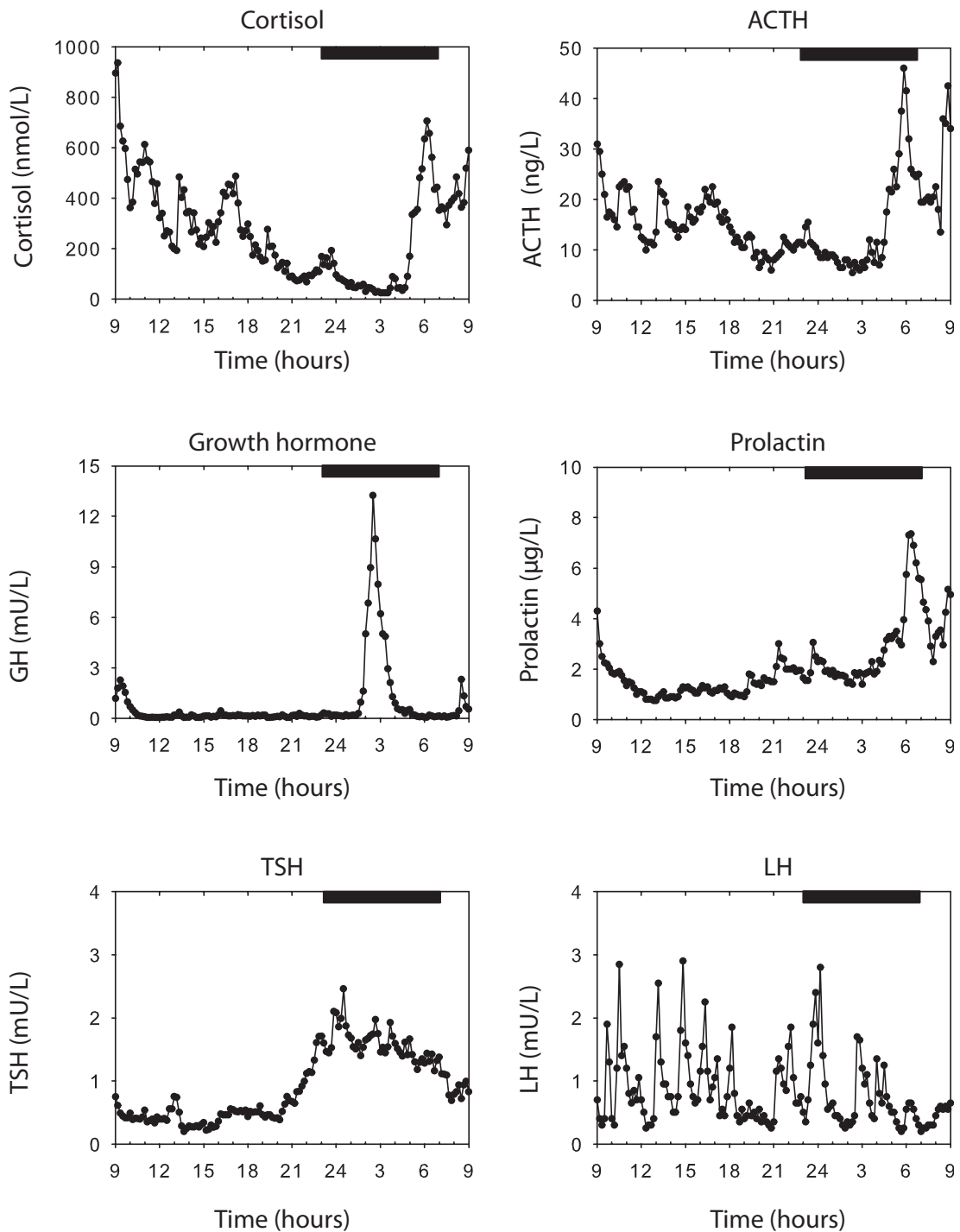
Figure 3. Plasma hormone concentration profiles of a 37 year-old healthy male volunteer. Blood samples were taken at 10 min intervals during 24 hours. The black bar in the top of the panels indicate the period with lights off. Note the diurnal and the pulsatile characteristics of each hormone. *(The figure was provided by Dr. F. Roelfsema, Leiden University.)*

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2.   Regulation of ACTH and cortisol secretion

The secretion of corticotropin (ACTH) and cortisol is regulated by hormonal interactions between the hypothalamus, pituitary, and adrenal glands. The secretion of hypothalamic corticotropin-releasing hormone (CRH) is regulated mainly by hippocampal neurons that express both receptors for cortisol, the mineralocorticoid- and glucocorticoid receptor. In addition the secretion is influenced by the circadian pacemaker and stress (2;11). CRH regulates the secretion of ACTH by the pituitary gland, which is potentiated by arginine-vasopressin. Subsequently ACTH binds to its receptor on the adrenal cortex to stimulate the secretion of cortisol and other steroids. The negative feedback loop is completed by the inhibitory effect of cortisol on CRH and ACTH synthesis and secretion (11).

Pulsatile secretion and circadian rhythm

ACTH is secreted in brief episodic bursts resulting in a diurnal rhythm of ACTH secretion with a concordant diurnal secretion of cortisol from the adrenal cortex (12;13). Plasma ACTH and serum cortisol concentrations are highest early in the morning at time of awakening. During the day plasma cortisol levels fall resulting in low levels in the late afternoon and evening with a nadir one or two hours after sleep onset (Figure 2 and 3) (11;14;15).

Stress-induced secretion

The HPA axis is activated both by physical and psychological stressors, resulting in increased plasma ACTH and cortisol concentrations. Physical stressors include severe trauma, like burns (16;17), or illnesses, major surgery (18;19), but also hypoglycemia (20;21), hypotension, exercise (22), and cold exposure (23).

Negative feedback inhibition by glucocorticoids

Both endogenous and exogenous glucocorticoids have a negative feedback on ACTH secretion which occurs at both the hypothalamic (CRH suppression) and pituitary (ACTH suppression) levels. This leads to atrophy of the adrenal glands resulting in loss of cortisol secretory capacity (24). The degree of probably depends upon the dose, potency and duration of action of the glucocorticoid, and the time of its administration (25–29). The shorter the interval between the

administration of glucocorticoid and the normal early morning peak of ACTH secretion, the greater the suppressive effect of the glucocorticoid. The duration of suppression is increased by higher doses and longer-acting glucocorticoids. After withdrawal of chronic administration of high doses of glucocorticoid, suppression of the hypothalamic-pituitary-adrenal axis may persist for weeks but may even persist for many years.

3. Regulation and secretion of thyroid hormone, gonadotropins and prolactin

The hypothalamus-pituitary thyroidal axis regulates the production of thyroid hormone by the thyroid gland. The hypothalamus produces thyroptropin releasing hormone (TRH) which stimulates the pituitary gland to secrete thyrotropin (TSH). TSH stimulates the synthesis of the thyroid hormones (thyroxine (T_4) and triiodothyronine (T_3)) by binding to the TSH receptors on the thyroid cells. The response of TSH to TRH is, in turn, modulated by the circulating concentrations of T_3 and T_4. High serum levels of T_3 and T_4 inhibit and low levels stimulate TSH synthesis (2).

The reproductive axis is controlled by periodic pulsatile release of the hypothalamic gonadotropin-releasing hormone (GnRH). GnRH stimulates the pituitary to secrete the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The production of steroid hormones (including estradiol, progesterone and testosterone), as well as other factors such as inhibin, activin and insulin-like growth factor-I (IGF-I) are induced by the gonadotropins. The circulating sex steroids have a positive as well as negative feedback on GnRH and thereby also influence LH and FSH concentrations.

The function of LH in men is to stimulate testosterone production from interstitial cells of the testes (Leydig cells) and FSH is required for spermatogenesis. In women, LH is critical for ovulation and maintenance of the corpus luteum, whereas FSH promotes follicular development (2).

The main physiological role of prolactin (PRL) is for nursing. The hypothalamic control of PRL secretion is predominantly inhibitory, and dopamine is the most important inhibitory factor. TRH is a potent prolactin-releasing factor (2).

III. Pituitary insufficiency

Hypopituitarism refers to decreased secretion of pituitary hormones, which can result from diseases of the pituitary gland and/or the hypothalamus, which cause diminished secretion of hypothalamic releasing hormones, thereby reducing secretion of the corresponding pituitary hormones. Pituitary insufficiency can be congenital (which will not be further addressed in this thesis) or acquired.

Pituitary adenomas and its treatment

A common cause of pituitary dysfunction is the presence of a pituitary adenoma. Macro-adenomas (> 10 mm) can be associated with pituitary insufficiency, with one or more anterior pituitary hormone deficiencies (30–32). In the presence of macroadenomas, hypopituitarism may result from compression of the rest of the pituitary and/or compression of the portal vessels in the pituitary stalk, secondary to either the expanding tumor mass or directly by increased intra-sellar pressure (30). Conversely, reduction of tumor mass by surgery and/or medication relieves the pressure and may restore pituitary function.

In pituitary surgery the surgeon attempts to preserve the adjacent normal pituitary tissue. However, if the surgeon is not able to visually distinguish the normal pituitary tissue from the adenoma, the normal tissue may be damaged, resulting in pituitary deficiency (33;34).

Radiation of pituitary adenomas, usually to prevent regrowth of residual tissue after surgery or to control excessive GH or ACTH secretion, also exposes the nonadenomatous pituitary and the hypothalamus to irradiation resulting in pituitary insufficiency (35;36). Not only patients with pituitary tumors but also patients treated with radiotherapy for suprasellar lesions, primary brain tumors, nasopharyngeal tumors, head and neck tumors, or hematological malignancies (*i.e.* acute lymphoblastic leukemia (ALL)) are at risk for developing pituitary hormone deficiencies if the hypothalamus and/or the pituitary have been exposed to radiation (37–39).

Traumatic brain injury

In recent years, several studies have reported a high prevalence of pituitary insufficiency ranging from 15–90% in patients who experienced traumatic brain injury (TBI) (40–51). Large neuropathological series demonstrate pituitary as well as hypothalamic lesions after TBI (52). Infarction is believed to be the cause of posttraumatic hypopituitarism, found at post mortem in 26% to 86% of patients who died after TBI. Possible mechanisms for post-traumatic infarction include compression of the pituitary gland caused by changes in intracranial pressure resulting from cerebral edema, hemorrhage or skull fracture, hypoxia, or direct damage to the gland itself (53;54).

The diagnosis of hypopituitarism, defined as deficient secretion of one or more pituitary hormones secondary to pituitary or hypothalamic disease, is made by documenting subnormal secretion of these pituitary hormones under defined (*i.e.* controlled) circumstances. Since there is a variable pattern of hormone deficiencies among patients with hypopituitarism, each pituitary hormone must be tested separately. For the evaluation of each axis basal serum hormones levels, but also dynamic testing is available.

Growth hormone deficiency

Clinical consequences

Growth hormone deficiency (GHD) in adults is characterized by increased body fat and decreased lean body mass, decreased bone mass and increased fracture rate, impaired cardiac function and reduced muscle strength (55–57). Adult patients with GHD also share a number of characteristics of the metabolic syndrome, including hypertension, abdominal obesity, insulin resistance and dyslipidemia (58). In addition, quality of life is impaired, with reduction in physical and mental energy, increased anxiety, and dissatisfaction with body image and poor memory (2;57;59;60). Replacement therapy with growth hormone (rhGH) was associated with apparent benefits, particularly in terms of body composition, bone mass, muscle strength, cardiac function and quality of life (61).

Diagnosis

Because of the pulsatile nature of GH secretion, basal serum GH levels are not useful to assess the GH-IGF-I axis, although basal serum IGF-I levels below the reference ranges are indicative for GHD in the presence of two or more other insufficiencies (62;63). Normal IGF-I concentrations, however, do not exclude the diagnosis of GHD, as IGF-I levels are within the normal reference range in about one third of patients with GHD, especially in elderly subjects (64–66). Therefore, the use of dynamic testing is mandatory for the evaluation of GH secretory reserve.

Different stimulation tests are available (*i.e.* insulin tolerance test (ITT), and stimulation tests with glucagon, GHRH, GHRH-arginine, or GHRH-GHRP6). However the preferred test for evaluation of this axis still remains the insulin tolerance test (63;67). With the administration of insulin a hypoglycemia is induced which is a very strong physiological stimulator of the stress response. Hypoglycemia activates the hypothalamus to secrete GHRH resulting in stimulation of GH by the somatotropic cells of the pituitary gland. A peak GH response below 3 µg/L indicates a severe GHD (63;67). During ITT simultaneous assessment of the hypothalamus-pituitary-adrenal (HPA) axis is possible. Important contra-indications to perform the ITT are coronary insufficiency and/or epilepsy. To assess the GH axis in these patients, alternative provocative tests for GH secretion must be used with adapted appropriate cut-offs. The combined administration of arginine and GHRH is the most frequently used alternative GH stimulation test (66;68;69). GHRH and arginine both have a stimulatory effect on the pituitary gland (70;71). When given simultaneously they enhance their effect resulting in a secretion of GH. A bolus dose of GHRH (1 µg/kg body weight) is given intravenously at baseline, immediately followed by an intravenous infusion of arginine (0.5 gr/kg body weight (to a maximum of 30 gr)) for 30 minutes. Measurements of GH are done 30, 45, 60 and 90 minutes after infusion. Recently, cut-off values adjusted for both body mass index (BMI) and age have been published (72).

Pitfalls

Several factors play a role when testing the GH secretion reserve, such as age, gender, BMI, other hormones and insulin sensitivity. Obese subjects have a blunted GH response to any provocative stimulus (8;73;74). There is an estrogen-related difference in GH axis activity: GH secreted per burst

greater and 24-hour GH release pattern is less orderly in women than men (75). Finally, GH secretion decreases with increasing age. Therefore, these factors should be considered when defining the diagnostic cut-off points in the assessment of GHD (72;76).

Corticotropin deficiency

Clinical consequences

ACTH deficiency leads to adrenocortical insufficiency, characterized by decreased secretion of cortisol. Normal corticotroph function is mandatory for adequate increase of cortisol concentrations in case of stress. However, to maintain sufficient cortisol concentrations, normal basal secretion of ACTH is necessary.

Hypocortisolism can be secondary to either adrenal gland destruction (primary adrenal insufficiency, mostly auto-immune adrenalitis or tuberculous adrenalitis) or to ACTH deficiency (secondary or central adrenal insufficiency) (77).

Diagnosis

Similar to the secretion of GH, the secretion of ACTH is pulsatile with circadian variation resulting in a circadian rhythm of cortisol secretion. Therefore, it is necessary to evaluate basal serum cortisol secretion in the early morning, during fasting. When cortisol concentrations are lower than, or exceed, a certain threshold (< 100 nmol/L or > 500 nmol/L) the likelihood of the presence or absence of adrenal insufficiency is very high, or negligible, respectively. In these cases stimulatory tests are not necessary (78). In all other condition, a dynamic test is mandatory.

The initial and most convenient test to evaluate the function of the HPA axis is the plasma cortisol response to synthetic ACTH (Synacthen test) (79;80). The test is performed by administering a bolus of 1 or 250 µg of cosyntropin intramuscularly or intravenously with measurements of serum cortisol 30 and 60 minutes thereafter. A serum cortisol concentration of ≥ 500–550 nmol/L is considered a normal response. However, this test does not discriminate between the different causes of adrenal insufficiency, and a normal test response does not exclude mild secondary forms of adrenal insufficiency (81–84).

Other tests, that directly evaluate pituitary reserve are also available (insulin induced hypoglycemia, metyrapone administration, or CRH stimulation). Also in the assessment of the HPA axis (similar to the GH-IGF-I axis) the ITT still remains the golden standard (85;86). Insulin induced hypoglycemia results in stress which actives the entire HPA axis providing proof for adequate hypothalamic (CRH) and pituitary (ACTH) function. In healthy subjects serum cortisol levels will increase above 550 nmol/L if adequate hypoglycemia is achieved (glucose 2.2 mmol/L or lower). Stimulation with metyrapone is an alternative test to assess the HPA axis. The adrenal enzyme 11-ß-hydroxylase (CYP11B1) that catalyzes the conversion of 11-deoxycortisol to cortisol, is inhibited by metyrapone, resulting in a reduction of cortisol secretion. Administration of metyrapone will thus result in activation of the HPA axis, an increase in ACTH secretion and consequently an increase in adrenal steroidogenesis up to 11-deoxycortisol. An 11-deoxycortisol concentration above 200 nmol/L in the presence of suppressed cortisol levels (below 100 nmol/L) is then indicative for central adrenal insufficiency (87–89). This test can be performed as a prolonged and short overnight version, depending on the number of dosages of metyrapone given. It appears, however, that the ACTH stimulus of a single dose of metyrapone is comparable to that of an insulin tolerance test (89).

Since the 1980's ovine CRH is used for the evaluation of the HPA axis, mainly to discriminate between pituitary or adrenal causes of Cushing's syndrome (90-94). However, in recent years the CRH test is more often used to assess secondary adrenal insufficiency (95;96). Administration of an intravenous bolus of ovine CRH results in pituitary ACTH secretion resulting in cortisol secretion by the adrenal glands. In healthy subjects a 1 µg/kg i.v. CRH bolus results in a peak ACTH response within 15 min and a peak cortisol response within 30–60 min. A peak cortisol of 550 nmol/L or higher is considered to be a sufficient reaction. The CRH test however, is inferior to the ITT and metyrapone test (97).

Pitfalls

The use of exogenous corticosteroids can suppress the HPA axis. Therefore, in case of exogenous glucocorticoid use, a reliable evaluation of the HPA axis can not be performed within 6 weeks after withdrawal of the steroid but might even be disturbed many months thereafter. Contraceptives in females should also be stopped for at least 6 weeks

because of the effects of hormonal agents on cortisol binding globulin (CBG) levels (98;99).

Thyrotropin deficiency

Clinical manifestation

The symptoms and signs associated with thyrotropin (TSH) deficiency are similar to those of primary hypothyroidism but usually are less severe, as there often is some residual thyrotropin secretion. In addition, TSH deficiency is almost always part of complete anterior pituitary hormone deficiency because thyreotroph secretion is the most resistant to insufficiency. Tiredness, cold intolerance, weight gain, constipation, dry skin, and hair loss are common features.

Diagnosis

TSH deficiency is diagnosed by low or normal serum TSH concentrations in the presence of low serum free thyroxine (fT_4) level. Measurement of serum fT_3 is not of additional value but may be low or normal. Thyrotropin-releasing hormone (TRH) can be used to assess TSH secretion. However, the response to TRH varies widely among individuals. Therefore it is not possible to discriminate between a normal and abnormal response in the majority of cases and TRH has not been incorporated into routine clinical practice of the evaluation of TSH deficiency (100).

Gonadotropin deficiency

Clinical manifestations

The clinical features of gonadotropin deficiency are determined by gender and the age of development. The physical examination in men with recent onset hypogonadism will usually be normal. However, in longstanding hypogonadism diminished facial and body hair, gynaecomastia, and small, weak testes can be present. Libido may be reduced and the ability to achieve and maintain an erection may be compromised. Patients can also complain of nonspecific symptoms, such as tiredness, reduced muscle strength, reduced exercise capacity, but also emotional lability and depression. The symptoms in men are nonspecific and therefore

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may not become evident for many years, particularly if fertility is not an issue (77).

In women gonadotropin deficiency leads to menstrual disturbances (*i.e.* oligomenorrhea or amenorrhea) and therefore often earlier diagnosed compared to men (2).

Diagnosis

The diagnosis in women is straightforward. In premenopausal women secondary amenorrhea with low levels of estradiol and low or nomal levels of gonadotropins will confirm the diagnosis. Whereas, in post-menopausal women FSH and LH will be (undetectably) low.

Low or normal gonadotropin levels combined with serum testosterone levels below the reference range, corrected for age are sufficient to confirm the diagnosis. Because of the great circadian variation randomly found decreased testosterone levels should be repeated in the early morning (between 8–9:00 AM).

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Prolactin deficiency

Clinical manifestations

Mild hyperprolactinaemia (up to 5 times the upper limit of normal) is common in patients with hypopituitarism. A pituitary mass with supra-sellar extension may compress the stalk resulting in decreased dopaminergic inhibition of prolactin secretion.

Raised prolactine levels effects pulsatile secretion of gonadtropins resulting in hypogonadism. Galacthorrhea can also be present. Prolactin deficiency almost invariably results from lactotroph deficiency secondary to hypothalamic damage as a result of irradiation and or surgery.

Diagnosis

The diagnosis of prolactin deficiency is straightforward using commercially available assays with gender adjusted reference ranges for the determination of prolactin concentrations. However, unless it is in the postpartum period, there are no clinical implications.

IV. Outline of this thesis

Pituitary insufficiency in the presence of a pituitary macroadenoma or after pituitary irradiation is frequently reported. In addition, pituitary insufficiency is increasingly reported after traumatic head injuries. The correct evaluation and interpretation, however, of the pituitary axes, and consequently, the potential therapeutical consequences are a matter of controversies. The studies reported in this thesis aim to provide better insight into the complexity of different endocrine tests used for the evaluation of possible pituitary insufficiency and in the treatment of patients with pituitary insufficiency.

The evaluation of pituitary function in patients after traumatic brain injury

Traumatic brain injury (TBI) has emerged as an important cause of hypopituitarism. However, considerable variations in the prevalence of hypopituitarism are reported. These variations can partly be explained by the severity of trauma and timing of hormonal evaluation, but may also be dependent on endocrine tests and criteria used for diagnosis of hypopituitarism. Therefore, in **chapter 2**, we performed a systematic review of the literature to critically compare pituitary function tests, and definitions of hypopituitarism in studies that assessed the long-term outcome of TBI on pituitary function.

Because of the great variation in prevalence rates reported and the great variation in endocrine assessments used, we decided to perform a cross-sectional study in the Netherlands of a large cohort of 112 TBI patients evaluated after long-term follow-up. We assessed the prevalence of pituitary insufficiency in our own large cohort of TBI patients using a standardized endocrine evaluation, described in **chapter 3**. In these patients, we also evaluated quality of life (QoL) using different QoL questionnaires.

Dynamic tests of pituitary function in other pituitary diseases

Pituitary adenomas and their treatment (*i.e.* surgery and/or radiotherapy) are also causes for pituitary insufficiency. Pituitary insufficiency is a complication that can be attributed to the tumor itself (compression) but also to the surgical approach and/or subsequent radiotherapeutical intervention. Therefore, accurate assessment of pituitary function is critical for appropriate management of patients with pituitary adenoma after surgery with or without irradiation. For many years, all patients in our hospital underwent a CRH stimulation test for the evaluation of the HPA axis shortly after pituitary surgery. In **chapter 4,** we describe a retrospective study that evaluated the clinical applicability of the CRH test directly after TS in our center.

The ITT, however, is considered the golden standard test for the evaluation of the HPA axis. In **chapter 5,** we describe a study on the long-term prevalence of adrenal insufficiency after transsphenoidal surgery for growth-hormone secreting pituitary adenomas using the ITT and CRH test in the majority of the patients. The reason for this evaluation was a recently published study that reported a remarkably high prevalence of adrenal insufficiency after surgical and/or medical treatment without postoperative radiotherapy in patients treated for acromegaly. Therefore, in our study, we evaluated the prevalence and incidence rate of adrenal insufficiency in 91 consecutive patients during long-term follow-up after successful transsphenoidal surgery for acromegaly.

In addition to patients with pituitary tumors, patients with nonpituitary intracranial and or nasopharyngeal tumors are treated by radiotherapy, in which the pituitary gland is involved in the radiation field. These patients are also at risk for pituitary insufficiency. To assess the prevalence of possible pituitary insufficiencies we performed a systemic literature search and meta-analysis focusing on the prevalence of pituitary dysfunction in adult patients treated with radiotherapy for nonpituitary tumors, which is described in **chapter 6**.

Treatment of GH deficiency

When growth hormone deficiency is diagnosed, the therapeutical consequences should be carefully evaluated, especially in certain conditions like obesity and during senescence where GH secretion overlaps with a GH deficient state. With increasing age, but also increasing BMI, GH secretion decreases. Therefore, the effects of treatment with rhGH in obesity and in the elderly diagnosed with GHD might be different.

Therefore, in **chapter 7,** we performed a structured review, to critically assess the available literature in order to evaluate the available evidence for treatments of elderly patients with GHD.

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