PATHOPHYSIOLOGY OF THE ENDOCRINE SYSTEM

The system hypothalamus – hypophysis

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The system hypothalamus – hypophysis can be divided into two particular systems with different relation between the hypothalamus and respective part of the hypophysis:

1) Hypothalamus – adenohypophysis (= anterior pituitary gland)
   The hypothalamus produces liberins and statins that get with blood through the vascular portal system (two capillary systems) and hypothalamus-pituitary stalk in the adenohypophysis, where they control production of anterior pituitary hormones. The adenohypophysis produces hormones acting on peripheral tissues (growth hormone, prolactin) and glandotropic hormones (adrenocorticotropin, thyrotropin, gonadotropins) control activity of peripheral glands (i.e. the adrenal cortex, thyroid gland, gonads).
2) Hypothalamus – neurohypophysis (= posterior pituitary gland)
   Hypothalamus (nc. supraopticus, nc. paraventricularis) synthetizes vasopressin (= antidiuretic hormone, ADH) and oxytocin that are transported by axons of the hypothalamic neurones producing these hormones passing through the hypothalamic-pituitary stalk (axonal transport) into the neurohypophysis that is only a place of their release into the blood.

The main hypothalamic liberins and statins are:
Liberins:

- corticoliberin (corticotropin-releasing hormone, CRH; corticotropin releasing factor, CRF)
- thyroliberin (thyrotropin-releasing hormone, TRH)
- somatoliberin (growth hormone-releasing hormone, GRH)
- gonadoliberin (gonadotropin-releasing hormone, GnRH)

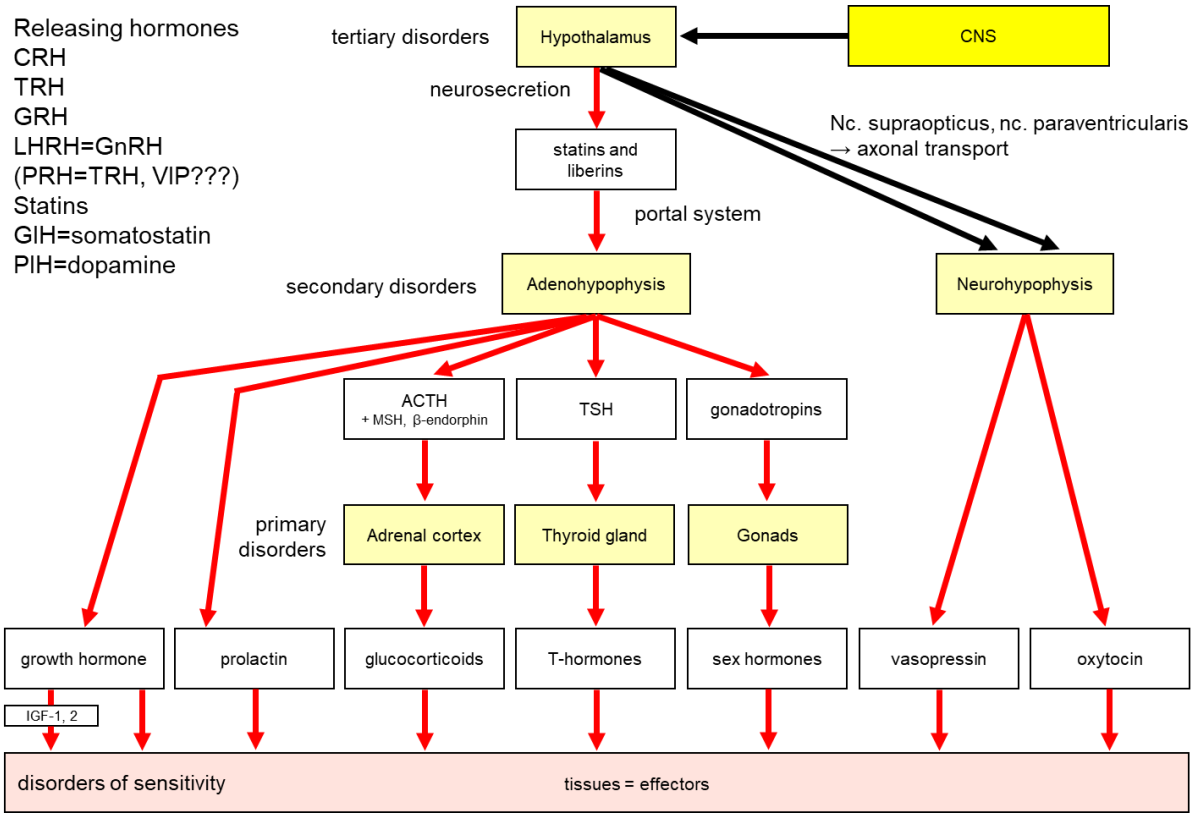
Statins:

- somatostatin (growth hormone-inhibiting hormone, GIH)
- dopamine (prolactin-inhibiting hormone, PIH)

Besides these main liberins and statins, there are (or are assumed) other substances playing a role in humoral control of the adenohypophysis by the hypothalamus having, however, less marked or only supplementary effects.
The list of the main liberins and statins shows that most of the anterior pituitary hormones are controlled only stimulating signals from the hypothalamus. Prolactin has, on the contrary, only inhibitory control. For growth hormone, there are both liberin and statin; nevertheless, somatoliberin has a stronger effect. Therefore, **if the adenohypophysis is completely devoid of hypothalamic control** (e.g. in interruption of the hypothalamic-pituitary stalk), **production**

of all anterior pituitary hormones declines (there is no stimulating effect of liberins) except for **prolactin secretion of which increases** (there is no inhibition by dopamine).

Scheme of the hypothalamus-hypophysis system



Hypothalamus

Among the endocrinological issues, the pathophysiology of the hypothalamus includes:

- Syndromes with complex symptomatology:
  - Fröhlich's syndrome = dystrophia adiposogenitalis
    - obesity, hypogonadisms, mental retardation
  - Laurence-Moon-Biedl's syndrome
    - obesity, hypogonadisms, retinitis, central diabetes insipidus
  - Prader-Willi's syndrome
    - obesity, mental retardation, short growth, hypogonadisms, cryptoracism
  - Kallmann's syndrome – olfactory and genital dysplasia
- Hypothalamus – neurohypophysis system (see below)
- Hypothalamus - adenohypophysis (see below)

Hypothalamus – neurohypophysis

Hormone synthesis in the hypothalamic nc. supraopticus and nc. paraventricularis:
- oxytocin, vasopressin (peptide hormones)

Hormones are transported via **axonal transport** into the neurohypophysis where they are released into the blood.

Oxytocin

Effects:
- contraction of the myoepithelial cells in the mammary gland ducts
- contraction of the myometrium during parturition
- importance for building a relationship between mother and child
- influence on behaviour – positive evaluation of another individual

Clinical importance of oxytocin: administered to promote uterus contractions during parturition

Vasopressin (antidiuretic hormone, ADH)

It acts on target tissues through several types of receptors with different effects:
V_{1A} – vasoconstriction
V_{1B} – increase of adrenocorticotropin (ACTH) secretion in the adenohypophysis
V_2 – transfer of aquaporins to the luminal membrane of kidney collecting duct cells

Regulation of ADH secretion
ADH secretion is increased by:
- high osmolality of extracellular fluid (osmoreceptors in the ventral hypothalamus)
- blood pressure decrease (hypovolemia acts via this mechanism)
- stress, physical exertion, pain (that are also stressors)

Diabetes insipidus
= insufficient effect of ADH in the kidney
It leads to reduced permeability of the collecting ducts for water, and thus to reduction of water resorption in this part of the renal tubular system. This results in the excretion of an increased amount (polyuria) of hypotonic urine, fluid loss with dehydration, hypovolemia, increasing the osmolality of the internal environment with relevant impacts on the functioning of the organism, eventually including death, if water loss is not replenished.
In case of absolute impermeability of the water collecting duct wall (i.e. in a complete absence of ADH) daily diuresis is about 20 l. This corresponds to the volume of tubular fluid flowing into the collecting ducts from the upper segments of the renal tubular system. This fluid is no longer subject to any resorption under these extreme pathological situations and leaves the body by urination. Of course, such fluid loss without proper replacement will endanger the body by dehydration and circulation failure very quickly. Frequent urination and thirst are less severe but annoying symptoms of diabetes insipidus

Diabetes insipidus has the following two variants:

Central diabetes insipidus
= lack of ADH, it is a disorder of ADH synthesis or leaching into the blood
Causes:
- Damage of the hypothalamus

- Damage of the neurohypophysis or hypothalamic-pituitary stalk – In this case, ADH deficiency is usually transient, and secretion to the blood recovers over time.
- Mutations in the ADH precursor (called propressophysin) encoding gene

Central diabetes insipidus can be treated with substitution therapy (ADH administration). Since this is a deficiency of ADH, not only its effect on the kidney but also its vasoconstrictive effects are missing.

Renal (peripheral) diabetes insipidus

= insensitivity of the kidney to ADH

Causes:

- Mutation in the V_2 receptor-encoding gene
- Mutation in the aquaporin-2-encoding gene
- Acquired disorders of tubule function in kidney diseases with reduced renal concentration ability.

Renal diabetes insipidus does not react on substitution therapy. Nevertheless, vasoconstriction effects of ADH mediated by another are preserved.

Syndrome of inappropriate ADH secretion (SIADH, Schwartz-Bartter syndrome)

Causes: ectopic secretion by a tumour (small cell lung cancer), brain damage

Increased ADH secretion leads to water retention. It increases extracellular fluid volume. The indirect consequence is a reduction in aldosterone secretion, which increases the loss of sodium and water via urine, and thus somewhat reduces water retention. However, sodium loss together with an increase in body water volume lead to hyponatremia with weakness, confusion, convulsions, and coma.

Water accumulation is also partially compensated by increased secretion of the atrial natriuretic peptide (ANP, the stimulus triggering its secretion is dilation of the heart atria during hypervolemia). Due to these secondary endocrine compensations, water accumulation is milder than would correspond to the level of ADH overproduction itself, and therefore there is usually no swelling.

Hypothalamus - adenohypophysis

This issue can be divided into 1) disorders of one or several hypothalamic liberins and statins and 2) disorders of the adenohypophysis.

Disorders of the hypothalamus (see above) include:

- Hypothalamic syndromes (Fröhlich's, Laurence-Moon-Biedl's, Prader-Willi's)
- Hypothalamic hypopituitarism
- Hyperfunction syndromes: tertiary hyperfunction syndromes (pubertas praecox...)

Disorders of the adenohypophysis include:

1. Hyperfunction states - adenoma
2. Hypofunction states – often panhypopituitarism
3. Dysfunction = combination of hyperfunction and hypofunction of several anterior pituitary hormones – tumour producing one of the hormones compresses the pituitary tissue, thereby disrupting the production of other hormones.

Enlargement of adenohypophysis e.g. by adenoma can cause intracranial hypertension and exert pressure on the chiasma opticum. In this case, the crossing fibres of the visual pathway from the nasal portions of the retina (i.e. temporal half-field of view) are affected. Thus, enlargement of the pituitary gland may also result in peripheral vision impairment.

Panhypopituitarism
= reduction of all adenohypophyseal hormones
Causes:
- trauma, tumour compressing the adenohypophysis, interruption of the pituitary stalk (but ↑ prolactin), Sheehan's syndrome = postpartum necrosis of the hypophysis due to shock

Manifestations and consequences of panhypopituitarism:
- lack of ACTH – reduced resistance to stressors
- anaemia, hypotension
- hypothyroidism
- hypogonadism
- growth retardation in children
- general atrophy = Simmonds cachexia

Pathophysiology of individual anterior pituitary hormones

Growth hormone (STH)

Growth hormone effects:
- acceleration of cartilage and bone matrix formation → growth
- increase of protein content and decrease of fat content in the body (proteoanabolic effect)
- synergistic action with ACTH in adrenal enlargement
- diabetogenic effect: increased glucose output from the liver, anti-insulin effect in the muscles

Thus, growth hormone accelerates growth in childhood and has anabolic and metabolic effects.
Some of the effects of STH on tissues are mediated by insulin-like growth factor 1 and 2 (IGF-1, IGF-2).

Regulation of growth hormone secretion:
- GRH and somatostatin - Hypothalamus or pituitary stalk lesions with lack of both of these hypothalamic hormones ultimately lead to a decrease in STH secretion.
- Negative feedback: IGF-1 inhibits STH secretion by the hypophysis and stimulates somatostatin secretion.

Stimuli increasing STH secretion:
- decrease in availability of substrates for energy generation (hypoglycaemia, starvation)
- physical exertion
- stress
- increase of some aminoacids in the blood (protein-rich food)

- falling asleep
- estrogens and androgens

Stimuli suppressing STH secretion:
- REM sleep
- glucose
- cortisol
- STH via negative feedback mediated by IGF-1

Lack of STH

– in a period of growth, it leads to proportional nanism (the size ratio of the individual body parts is maintained)

Laron nanism
- insensitivity to STH
- normal or even increased STH level

Excess of STH

1. In children → gigantism
- Before closure of bone growth clefts when bone growth to length is possible
- Stimulation of differentiation of prechondrocytes into chondrocytes → autocrine production of IGF-1 – chondrocyte proliferation → growth - The result is a high growth of the individual.

2. In adulthood → acromegaly
- After closing the bone growth clefts, when bone extension is no longer possible
- However, bones can grow in width, resulting in facial changes (enlargement of superciliary arches, nose, etc.), the circumference of the head, arms and legs increases
- This may result in a change in the distribution of the load on the joint surfaces and acceleration of their degenerative changes.
- Macroglossia, cardiomegaly, liver enlargement – changes in internal organs may lead to impaired function (the heart!)
- Fatigue, muscle weakness – muscle tissue becomes more massive, but is not fully functional
- Decreased glucose tolerance (hyperglycemizing effect of STH), hypertension, cardiomyopathy

Organ and metabolic changes can lead to severe health complications of the acromegaly.

Prolactin

Prolactin stimulates breast milk production. It inhibits gonadoliberin secretion in the hypothalamus, inducing hypogonadism and infertility and amenorrhea in women. The evolutionary advantage of this phenomenon is a reduction in the probability of pregnancy during lactation.

Prolactin secretion is inhibited by hypothalamic PIH, which is dopamine.

Galactorrhoea-amenorrhea syndrome

= a consequence of increased prolactin level

Causes:
- prolactinoma (prolactin-producing pituitary tumour)

- interruption of the hypothalamic-pituitary stalk (see above) – prolactin hypersecretion in combination with a decrease in other adenohypophyseal hormones
- dopamine receptor blocking – Dopaminergic receptor blockers are used to treat schizophrenia; an adverse effect may be an increase in prolactin levels.

Manifestations:
- Galactorrhoea = breast milk production outside pregnancy and lactation
- Amenorrhea = menstruation bleeding halting – a consequence of suppressing the menstrual cycle from inhibiting gonadoliberin secretion by prolactin

Pathophysiology of glandotropic pituitary hormones

Disorders of peripheral glands controlled by the hypothalamus axis - adenohypophysis - peripheral glands are divided into:

- **Primary** – the disorder primarily affects the peripheral gland, reducing or increasing its hormone production is therefore a primary change, changes in secretion of hormones of higher levels (hypothalamic, adenohypophyseal) are only a secondary response within the negative feedback. It means that in primary hypofunction of the gland, there is a secondary increase of glandotropic adenohypophyseal hormone and corresponding hypothalamic liberin (in the case of statin vice versa). The damaged peripheral gland is unable to respond adequately by increasing its hormone production to the administration of the pituitary glandotropic hormone. In primary gland hyperfunction, the situation is reversed (i.e. decrease of production of stimulating hormones of higher levels of the axis).
- **Secondary** – the disorder affects the adenohypophysis, alteration of the secretion of a particular adehohypophysial glandotropic hormone (or several hormones) causes a change in the function of the respective peripheral gland. If it is secondary peripheral gland hypofunction, the gland is capable of responding by increasing hormone production to the administration of the respective glandotropic hormone. However, there is no response to hypothalamic liberin administration (because adenohypophysis does not work).
- **Tertiary** – the disorder affects the hypothalamus, alteration of secretion of one of the hypothalamic statins and liberins (or more of them) results in a change in the activity of the adenohypophysis and a change in the production of the relevant pituitary glandotropic hormone (or hormones). Changing its level then changes the function of the peripheral gland. If it is tertiary hypofunction of the peripheral gland, the gland is able to respond by increasing the production of hormone to the administration of the relevant glandotropic pituitary hormone as well as to the administration of the appropriate liberin (peripheral gland and adenohypophysis work, the problem is lack of hypothalamic hormone).

The pathophysiology of individual glandotropic pituitary hormones is discussed in chapters devoted to individual peripheral glands controlled by adenohypophyseal hormones (the thyroid gland, adrenal cortex, gonads).