PROCEEDINGS OF THE GERMAN SOCIETY FOR NEUROSURGERY

MODERN ASPECTS OF NEUROSURGERY

VOLUME 4

I. THE PERIPHERAL VISUAL PATHWAY

II. PITUITARY TUMORS

III. VARIA

PROCEEDINGS OF THE 23rd ANNUAL MEETING HELD IN HAMBURG, SEPTEMBER 25–27, 1972

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1973

EXCERPTA MEDICA AMSTERDAM

AMERICAN ELSEVIER COMPANY, INC. NEW YORK

International Congress Series No. 306
ISBN Excerpta Medica 90 219 0249 4
ISBN American Elsevier 0 444 15104 4
Library of Congress Catalog Card Number 73-152681

Publisher
Excerpta Medica
335 Jan van Galenstraat
Amsterdam
P.O. Box 1126

Sole Distributors for the U.S.A. and Canada
American Elsevier Publishing Company, Inc.
52 Vanderbilt Avenue
New York, N.Y. 10017

Printed in The Netherlands by N.V. Drukkerij Trio, The Hague

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CONTENTS

III. VARIA

ENDOCRINOLOGY OF THE HYPOTHALAMUS AND THE PITUITARY GLAND*

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At present, the endocrinology of the hypothalamus and the pituitary gland has two main aspects with respect to tumors of this region: (1) the observation of endocrine symptoms permits the diagnosis of a tumor at an early stage, and (2) hormonal overproduction or deficiency must be evaluated, since therapy by ablative or substitutive measures is of considerable importance for the well-being and life expectancy of these patients.

PATHOPHYSIOLOGICAL CONSIDERATIONS

The rapidly growing information about the hormones of the hypothalamus and pituitary gland has recently been reviewed in a textbook of pathophysiology (Scriba et al., 1972). Today, the blood levels of the hormones of the human *anterior pituitary* (Table I) are determined radioimmunologically. Determination of the levels of growth hormone (GH) and of the glycoproteohormones TSH, LH and FSH is most commonly carried out by endocrinologists. The structures of the human glycoproteohormones are not yet fully analyzed; their subunits α and β (Table I) are just gaining attention as pathogenic factors and for diagnostic questions, whereas the human pituitary proteohormones, except for prolactin, have been synthesized.

Since the *posterior pituitary* is the subject of further communications during this conference, it may be permitted just to mention briefly the functional separation of the secretion of antidiuretic hormone (ADH) and thirst. Table II gives a summary of dissociated and combined disturbances of ADH secretion and thirst.

In recent years the concept of *hypothalamic hypophyseotropic hormones* has been introduced into clinical endocrinology. In Table III the releasing and inhibiting factors so far known are reported, together with the structures of 4 of these factors. Synthetic TRH (thyrotropin releasing hormone) and LH-RH (LH releasing hormone) have recently been employed for diagnostic and therapeutic purposes.

The secretion of the hypophyseotropic hormones is itself influenced by *hypothalamic catecholamines* (neurotransmitters). Kamberi et al. (1971) have shown by in vitro and in vivo experiments that dopamine stimulates LH secretion in rats via increased LH-RH secretion. In man *L-dopa* must be used since L-dopa, in contrast to dopamine, can cross the blood-brain barrier and serves as a precursor for dopamine and norepinephrine. Intravenous injection of L-dopa in patients does not increase the LH levels, as expected from animal experiments (Souvatzoglou et al., 1973). There is, however, a marked increment in *growth hormone* levels, presumably due to increased secretion of hypothalamic GRF after giving L-dopa intravenously. On the other hand, *prolactin* levels are diminished by L-dopa (Malarkey et al., 1971), apparently because of increased secretion of prolactin inhibiting factor (PIF). With PIF deficiency increased prolactin secretion is observed (Turkington et al., 1971), as neurosurgeons are well aware from the galactorrhea that follows pituitary stalk section.

In Figure 1 a scheme is given of the vertical functional relations between the groups of

* Supported by the Deutsche Forschungsgemeinschaft (SFB 51).

TABLE I

Human anterior pituitary hormones

Symbol	Name	Molecular weight	Amino acids	Carbohydrate (%)	Biological assay	Normal* plasma values		Plasma half-life
						Biological assay	Radioimmunoassay	
a. Proteohormones:								
ACTH	Adrenocorticotropic hormone, corticotropin	4600	39	—	Corticosterone secretion into the adrenal vein of hypophysectomized rats	0–5 μU/ml (9 a.m.)	<1–50 pg/ml (8–10 a.m.)	Exogenous 5–13 min; endogenous longer
β-MSH	Melanocyte stimulating hormone	2700	22	—	Pigmentation of frog skin	?	20–110 pg/ml	?
HGH = STH	Human growth hormone = somatotropin	21500	190	—	Epiphyseal cartilage of tibia, hypophysectomized rats	?	<1–5 ng/ml	Endogenous 50 min
HPr	Prolactin	22550 (ovine)	198	—	Pigeon crop	?	20–37 ng/ml	30 min
*b. Glycoproteohormones:***								
TSH	Thyroid stimulating hormone	25000 (bovine)	α 96 β 113	15	^{131}I-secretion of mouse thyroid	166 μU/ml ?	0.6–4.2 μU/ml	Exogenous 68 min; endogenous 90–130 min
FSH	Follicle stimulating hormone	32000 (ovine)	?	15	Augmentation of HCG effect on rat ovaries	—	4 mIU/ml**	Initial phase 4 hrs
LH = ICSH	Luteinizing hormone = interstitial cell stimulating hormone	30000 (ovine)	α 96 β 120	18	Ascorbic acid depletion, ovaries	—	13 mIU/ml**	Initial phase 1–2 hrs

* Normal plasma values depend on the definition of normal conditions: hour of the day, nutrition, age, sex and other factors have substantial influences.
** Values for normal young men in mIU IRP–2–HMG/ml serum; cyclic patterns are observed in women.
*** Glycoproteohormones have two chemically different subunits (M ~ 15000). Recombination experiments revealed that TSH-α, FSH-α and LH-α may be substituted; therefore the β subunits determine biological and immunological specificity. The amino acid sequences of LH-α, LH-β (ovine), of TSH-α, TSH-β(bovine) and the structure of the carbohydrate units of HCG-α and HCG-β are published; the carbohydrate units of the glycoproteohormones are linked to aspartic acid.
(From Scriba et al., 1972.)

TABLE II

Disorders of ADH secretion and thirst

ADH secretion	Thirst	Clinical manifestations
Absent even after induction of hypernatremia by water deprivation	*Normal*	*Classic diabetes insipidus* (polyuria and polydipsia)
Elevation of 'osmotic threshold' for ADH release	Normal	'Diabetes insipidus', urinary osmolality increases only after marked hypernatremia
Normal	*Decreased or absent*	*Adipsia*, hypernatremia without polyuria
Elevation of 'osmotic threshold' for ADH release	*Decreased or absent*	*Hypernatremia*, syndrome of *hypodipsia* and *ADH-reset*
Absent even in presence of hypernatremia	*Decreased or absent*	Severe *hypernatremia* without polyuria, *adipsia*
Normal	*Increased*, decreased osmotic threshold for thirst	*Primary polydipsia*, psychogenic polydipsia has to be differentiated
Inappropriately increased	Normal	*Hyponatremia* SIADH, syndrome of inappropriate ADH secretion (Schwartz-Bartter)

(After Mahoney and Goodman, 1968.)

TABLE III

Hypophyseotropic hormones – 'releasing factors'*

Hypophyseotropic hormone		Structure
CRF	= Corticotropin releasing factor	——
MSH-RF	= MSH releasing factor	——
MIF	= MSH inhibiting factor	Pro-Leu-Gly-NH_2
GRF	= GH releasing factor	Val-His-Leu-Ser-Ala-Glu-Glu-Lys-Glu-Ala?
GIF	= GH inhibiting factor	——
PRF	= Prolactin releasing factor	——
PIF	= Prolactin inhibiting factor	——
TRF	= Thyrotropin releasing factor	pyro-Glu-His-Pro-NH_2
LRF	= LH releasing factor	pyro-Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2
FRF	= FSH releasing factor	——

* Instead of the abbreviation RF (releasing factor) RH may be used, e.g. TRH = thyrotropin releasing hormone.
(From Scriba et al., 1972.)

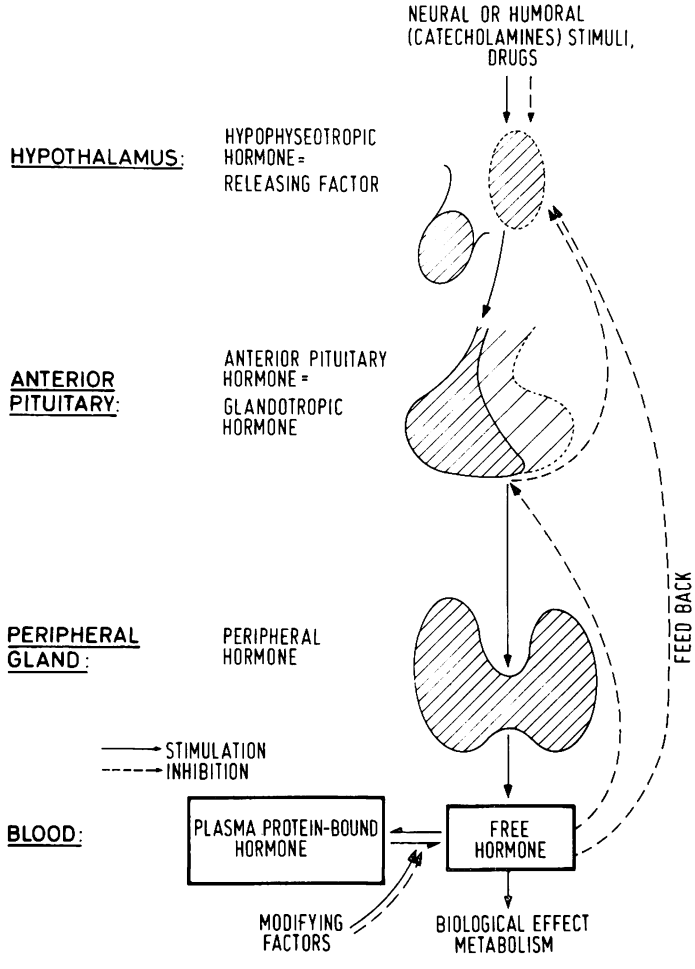

Fig. 1. Regulation of anterior pituitary hormone secretion. (From Scriba et al., 1972.)

hormones briefly discussed above. Hypothalamic catecholamines and hypophyseotropic hormones, together with the glandotropic hormones of the anterior pituitary, regulate the secretion of the peripheral target glands. The free, non-protein bound, i.e. biologically active, component of the hormones of the peripheral target glands is the parameter regulated by the glandotropic hormones ACTH, TSH and gonadotropins. Measurable alterations in the vertical hormonal axes serve for the regulation of the free peripheral hormones.

Tumors of the hypothalamic-pituitary region may lead to a deficiency in hypophyseotropic hormones, with consequent hypopituitarism, or alternatively may directly produce a deficient secretion of pituitary hormones with secondary insufficiency of the target glands (Fig. 1). In contrast to these forms of hypopituitarism in cases of inactive tumors, hormonal overproduction is found in *hormonally active tumors:* thus, the growth hormone excess of a pituitary adenoma causes acromegaly, while hamartomas of the tuber cinereum may produce pubertas praecox by increased LH-RH secretion.

DIAGNOSTIC IMPLICATIONS OF TESTS FOR HYPOTHALAMIC AND PITUITARY FUNCTION

This section briefly reviews the information which neurosurgeons may obtain from examination of hypothalamic and pituitary function. Table IV summarizes horizontally the site of action and vertically the effective scope of the endocrinological methods.

In clinically evident hypopituitarism the determination of *basal levels* of pituitary and target gland hormones will not always reveal subnormal values. This is for methodological reasons, since the analytical procedures do not always permit a distinction between the wide normal ranges of controls and the lowered values of these patients. Thus, in cases of complete or incomplete 'panhypopituitarism', normal or subnormal basal hormone levels may be found. Therefore, as a general endocrinological rule, *stimulation tests* are employed for the diagnosis of insufficiency states and *suppression tests* for hormonal overproduction states.

Stimulation tests are available for the examination of disorders of the hypothalamic-pituitary region. These act on the site of the *hypothalamus* and on the *anterior pituitary*. The technical problems of all these tests have recently been discussed at length in the endocrinological textbook of Labhart (1971) and will not be dealt with here. As a first example the *insulin hypoglycemia test* (Table IV) will be mentioned, in which the control person reacts with an increased secretion of growth hormone. This test is of particular value in the diagnosis of pituitary insufficiency, as discussed by Fahlbusch during this meeting (pp. 90–95). The same procedure, the insulin hypoglycemia test, also provides a means to test the *CRF-ACTH-cortisol* axis and to assess the ability of a patient to tolerate *stressful situations*.

A decreased response to this test may be due to an insufficiency at one or more of the levels mentioned, namely hypothalamus, adenohypophysis or adrenal gland. In this case lysin-vasopressin is used as a corticotropin releasing factor (CRF) for further eludication. A positive response to lysin-vasopressin, i.e. increase of radioimmunologically determined ACTH levels or of cortisol levels, reveals intact corticotropic function of the adenohypophysis and locates the disorder in the suprasellar region. Lysin-vasopressin may also be used for the differential diagnosis of Cushing's syndrome, since no response is found in cases caused by adrenal tumors in contrast to cases of hypothalamic-hypophyseal origin (Scriba et al., 1972). The CRF-ACTH-cortisol axis is, however, only of limited value for the *differentiation* between *hypothalamic and hypophyseal disorders*, since only a small proportion of patients with tumors in the hypothalamic-hypophyseal region have secondary adrenal insufficiency.

In the next axis (Table IV) synthetic TRH is used for the stimulation of *TSH secretion* by the adenohypophysis. This test provides information about the suprasellar extension of pituitary tumors (Pickardt et al., *This Volume*, pp. 105–107). However, no means yet exist for specifically stimulating the secretion of endogenous TRH, as antithyroidal drugs – and other inhibitors as well, e.g. Metopirone (Table IV) – act on the adenohypophysis and the hypothalamus simultaneously. Synthetic LH-RH has recently been employed to stimulate the secretion of both *gonadotropins (LH, FSH)* at the pituitary level, whereas clomifene apparently acts via increased secretion of hypothalamic endogenous LH-RH. The clomifene stimulation test has, however, the disadvantage of a lag time of some days (Souvatzoglou, personal communication).

After these considerations we have briefly to come back to the tests for secretion of the directly acting adenohypophyseal hormones GH and prolactin. In addition to the insulin hypoglycemia test (l.a.) it is possible to stimulate *growth hormone* secretion at the hypothalamic level using intravenous L-dopa injection (Souvatzoglou et al., 1973), which at the same time lowers the prolactin levels (l.a.). Since TRH stimulates the secretion of *prolactin* as well as of TSH, the former hormone may be checked at both the hypothalamic and the adenohypophyseal level.

The aims of *endocrinological examination* of patients with *hypopituitarism* may be summarized as follows:

1. Detection of hormonal deficiencies and estimation of the necessary substitutive therapy.
2. Assessment of stress tolerance.
3. Differentiation of hypothalamic and adenohypophyseal hypopituitarism.
4. Differentiation of primary and secondary insufficiency of target glands.
5. Stimulation tests at the hypothalamic and hypophyseal levels may in addition provide

TABLE IV

Site of action and effective scope of endocrinological methods for the investigation of hypothalamic and pituitary disorders

1. *Basal hormone levels*					
Determination of (glandotropic) anterior pituitary hormones	ACTH	TSH	LH, FSH	Growth hormone	Prolactin
Determination of peripheral hormones	Cortisol (circadian rhythm!)	Thyroxine, triiodothyronine	Testosterone, estrogens, progesterone	—	—
2. *Stimulation tests*					
Stimulation of the axis hypothalamus-pituitary-peripheral gland	Insulin hypoglycemia	—	Clomifene	Insulin, hypoglycemia, arginine, L-dopa	Phenothiazine ↑ L-dopa ↓
Withdrawal of peripheral hormones = stimulation of hypothalamus-pituitary	Metopirone	Antithyroid drugs	(Anti-androgen)	—	—
Stimulation of the anterior pituitary with hypophyseotropic hormones	Lysin-vasopressin (as CRF)	TRH	LH-RH	—	TRH
Stimulation of peripheral glands with glandotropic hormones	ACTH stimulation test	TSH stimulation test	HCG stimulation test	—	—
3. *Suppression tests*					
Hypothalamus-pituitary	Dexamethasone	T_3 suppression test	—	Oral glucose tolerance test	(Ergot-alkaloids)

(From Scriba et al., 1972.)

information about the suprasellar extension of pituitary tumors.

Finally, *suppression tests* must briefly be mentioned (Table IV), as these are used in cases with hormonal overproduction (Fahlbusch, *This Volume*, pp. 90–95). Oral glucose tolerance tests suppress growth hormone secretion in normals and in chemical diabetes. In view of the multiplicity of factors that stimulate growth hormone secretion (Scriba et al., 1972), and taking borderline cases into account, the GH suppression test by oral glucose loading is of importance in the diagnosis of acromegaly. Absent or paradoxical GH responses to the tests (oral glucose tolerance, arginine tolerance, insulin hypoglycemia) demonstrate the functional autonomy of growth hormone producing adenomata of the adenohypophysis. In general, these tests are of particular importance for the assessment of the success of therapeutic measures in cases of hormonally active tumors.

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