Treatment of Pituitary Adenomas

First European Workshop on Treatment of Pituitary Adenomas at Rottach-Egern

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336 Figures, 85 Tables

Georg Thieme Publishers Stuttgart 1978

CIP-Kurztitelaufnahme der Deutschen Bibliothek

Treatment of pituitary adenomas / 1. Europ. Workshop on Treatment of Pituitary adenomas at Rottach-Egern, October 1976. Ed. by Rudolf Fahlbusch and Klaus v. Werder. With contributions by H.-P. Althoff ... – 1. Aufl. – Stuttgart : Thieme; Massachusetts : PSG Publishing Company, 1978.

ISBN 3-13-553801-X (Thieme)
ISBN 0-88416-236-2 (PSG)

NE: Fahlbusch, Rudolf [Hrsg.]; Althoff, H.-P. [Mitarb.]; European Workshop on Treatment of Pituitary Adenomas <01, 1976, Rottach-Egern>

Thieme: ISBN 3-13-553801-X
PSG: ISBN 0-88416-236-2
PSG: LCCCN 77-99148

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Short contributions

OPERATIVE TREATMENT

Physiology of the Hypothalamo-Pituitary Unit

P.C. Scriba, C.R. Pickardt and K. von Werder, Munich, FRG

Biogenic amines and hypophysiotropic hormones from the hypothalamus regulate the secretion of the anterior pituitary hormones. These, in turn, control the target glands (adrenals, thyroid, gonads) as far as the glandotropic hormones (ACTH, TSH and gonadotropins) are concerned. This system is subject to negative and, in some cases, positive feedback control through the free fractions of the circulating peripheral hormones (cortisol, thyroid hormones, sexual steroids). Some anterior pituitary hormones (growth hormone, prolactin) and the neurohormones from the posterior pituitary (antidiuretic hormone, oxytocin) exert their effect directly on the peripheral tissues and organs. A complete evaluation of this system would probably fill a textbook [21], this review will therefore be limited to some selected aspects.

The Traditional Interest of Neurosurgeons in Endocrinology

The clinical course of pituitary tumors may be beneficially influenced by a close observation of endocrine signs and symptoms, permitting an early diagnosis of hormonally active or inactive tumors. In the case of inactive tumors, earlier observations (19) revealed that half of the patients showed hypogonadism as a first symptom in their histories; on the other hand in 32 of 42 patients the neglecting of this sign resulted in delay of the diagnosis until deterioration of the visual fields set in. Today, in cases of prolactinoma [27], the female patients (N = 43) with a lower prolactin level tend to outnumber the males (N = 22). This is presumably due to an earlier diagnosis in the case of the females, because amenorrhea and galactorrhea are obviously more impressive endocrine signs than loss of libido and potence.

There is yet another case for endocrinology which should be brought up in this context. Table 1 shows the sites of action and the range of hormonal diagnostic procedures [20, 21]. With reference to the paper of Solbach et al. [22], we should like to emphasize briefly the principle of diagnostic floors – in German "Etagen-Diagnostik". In general, insulin hypoglycemia will stimulate at the hypothalamic level, whereas releasing hormones may indicate an insufficiency of the anterior pituitary and TSH-stimulation, for instance, will test the responsiveness of the target thyroid gland. The site of action is generally less clear if suppression tests have to be used for the differential diagnosis of hormone overproduction states (Table 1).

Laboratory Methods

Most of the diagnostic hormone determinations are nowadays performed by radioimmunoassay. Radioimmunoassay procedures have, in fact, contributed enormously to the knowledge we have today of the pathophysiology of the hypothalamo-pituitary unit.

And yet by far not all methodological questions have been solved statisfactorily in this field.

Studies by Leidenberger et al. [10] showed that the LH-values differed considerably in postmenopausal women when determined by radioimmunoassay or radioreceptorassay. The ratio of the radioreceptorassay result over radioimmunoassay result was

Table 1 Site of Action and Range of Endocrinological Methods for the Investigation of Hypothalamic and Pituitary Disorders (from Scriba and von Werder [21])

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	Somatomedins	–
2. *Stimulation tests*					
Stimulation of the axis hypothalamus-pituitary-peripheral gland	Insulin-hypoglycemia	–	Clomifene	Insulin-hypoglycemia, arginine,	Insulin-hypoglycemia, Phenothiazine
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	Bromocryptin

higher than ten in some sera. Since the radioreceptor levels agreed with a sensitive in-vitro bioassay, it may be concluded that the radioimmunoassay of LH in serum retains unsolved problems of accuracy at least in terms of the biological significance of what is measured.

The interlaboratory comparison of radioimmunoassays for TSH performed by the German Thyroid Association may be regarded as another example for methodological problems [11]. The value for one sample varied widely around a mean of 22.9 μU with an interlaboratory coefficient of variation of 64%. The results of the group were improved to a more accurate mean of 17.3 μU (coefficient of variation = 22%), when standards in hormone-free serum were used as a reference for all participants. Figure 1 provides further information about the accuracy for the radioimmunoassay for TSH [1]. Regular-size TSH preparations and various big TSH preparations from human pituitaries show corresponding values when analyzed by radioimmunoassay and by cytochemical bioassay, i.e. no major descrepancies have been observed so far between radioimmunoassay and bioassay for the determination of TSH. However, certain aspects of

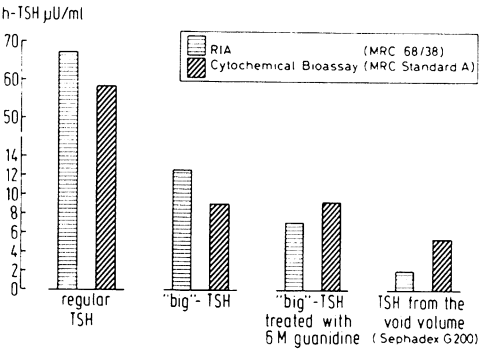

Fig. 1 Comparison of immunological and biological thyrotropin activity in preparations of regular TSH and "big"-TSH (from Erhardt and Doehler [11])

the methods for the quantitative determination of pituitary hormones obviously require continued attention.

The Radioimmunoassay for TRH

With regard to the determination of hypothalamic releasing hormones, I should like to refer to the recent work of Mitsuma et al. [12]. These authors have apparently developed a radioimmunoassay procedure which permits the analysis of TRH in peripheral serum. It is interesting to note that TRH levels appear to be low in hyperthyroidism. This would favor the early concept of a negativ feedback regulation of TRH secretion by thyroid hormones, a concept challenged by the studies of Reichlin et al. [18] and Oliver et al. [15]. This TRH assay [12] might even be useful for the differentiation between hypothalamic and pituitary forms of secondary hypothyroidism.

TRH Stimulation Tests

In recent years releasing hormones have been applied widely for diagnostic stimulation tests. The normal specificity of TRH, for instance, in stimulating TSH and prolactin secretion has been repeatedly documented. This specificity may be altered in cases of pituitary adenomas which produce growth hormone or prolactin; TRH may now stimulate growth hormone secretion. On the other hand, the stimulatory effect of TRH on the lactotroph may be lost in cases of adenoma [26]. The concept of "receptor degeneration" in pituitary adenomas will be dealt with in greater detail later on.
The TRH-stimulation test may even provide insight into localization and extension of tumors in the hypothalamo-pituitary region. As reported previously [17], nine patients with secondary hypothyroidism and suprasellar disease showed a normal or exaggerated TSH response to TRH stimulation. However, a normal or exaggerated TSH response was also found in all patients but one with secondary hypothyroidism due to a hormonally inactive pituitary adenoma. It was concluded from this surprising observation, that the hypothyroidism in these cases was a result of suprasellar extension of the pituitary adenoma, leading to portal vessel occlusion or to direct interference with hypothalamic TRH-production [17]. A suprasellar extension may thus be anticipated in patients with a pituitary tumor, secondary hypothyroidism and TRH-responsive TSH secretion.

Fahlbusch and Pickardt [2] continued the work along these lines. Table 2 compares the TSH increase after intravenous and intraventricular TRH application, respectively, du-

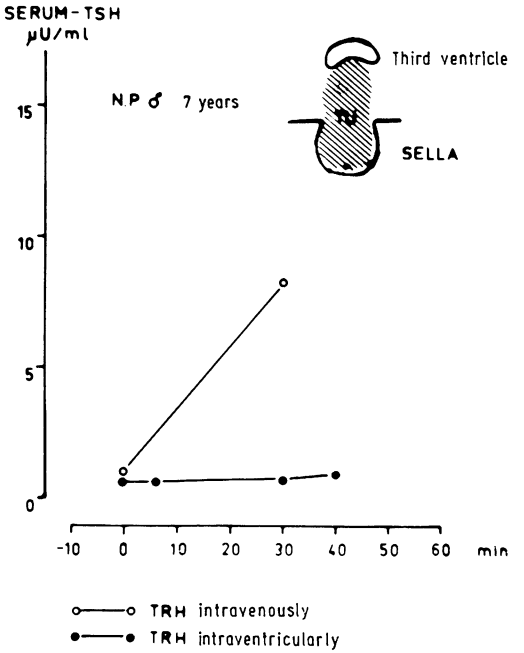

Fig. 2 Inhibition of TRH transport from the third ventricle to the anterior pituitary in a patient with pituitary adenoma (cf. text; from Fahlbusch and Pickardt [2])

ring a diagnostic puncture of the lateral ventricle. The far right column represents the control TSH response to intraventricular TRH. In contrast, the patient referred to in Fig. 2 did not respond to intraventricular TRH, but showed a perfectly normal TSH increment after intravenous TRH. These findings support the assumption that it may well be the interference with the TRH transport from the third ventricle [16, 17] or, respectively, from the hypothalamus to the anterior pituitary which causes secondary hypothyroidism in patients with suprasellar extension of pituitary adenomas.

Table 2 Increase in Serum TSH Concentration (μU/ml) after Intravenous and Intraventricular Administration of 50μg of TRH (from Fahlbusch and Pickardt [2])

	intravenous		intraventricular							i.venous	i.ventricular
min →	0′	30′	0′	5′	10′	20′	30′	40′	60′	ΔTSH at 30′	
R.D.	2.4	12.5	4.1	3.1	3.2	5.0	*6.1*	6.1	6.0	10.1	2.0
M.M.	2.6	16.2	1.3	1.3	1.7	2.7	4.5	*6.3*		13.6	3.2
E.J.	1.1	6.4	1.8	2.0	2.6	3.8	6.8	9.3	*11.1*	5.3	5.0
R.F.	1.8	19.9	2.5		3.1	5.8	9.8	13.8	*17.5*	18.1	7.3
W.P.	4.3	20.8	3.2		4.5	10.0	*13.2*	12.8		16.5	10.0

On the Regulation of TSH Secretion

Fig. 3 gives the last example of TRH pathophysiology I should like to discuss. In this study of Horn et al. [8], the effect of repeated oral administration of 40mg TRH to a control group is shown. The first oral TRH administration resulted in the expected increase in TSH and prolactin. At the same time, the T_4 and T_3 levels were slightly raised towards the upper limit of normal, and T_4 remained on the borderline, in accord-

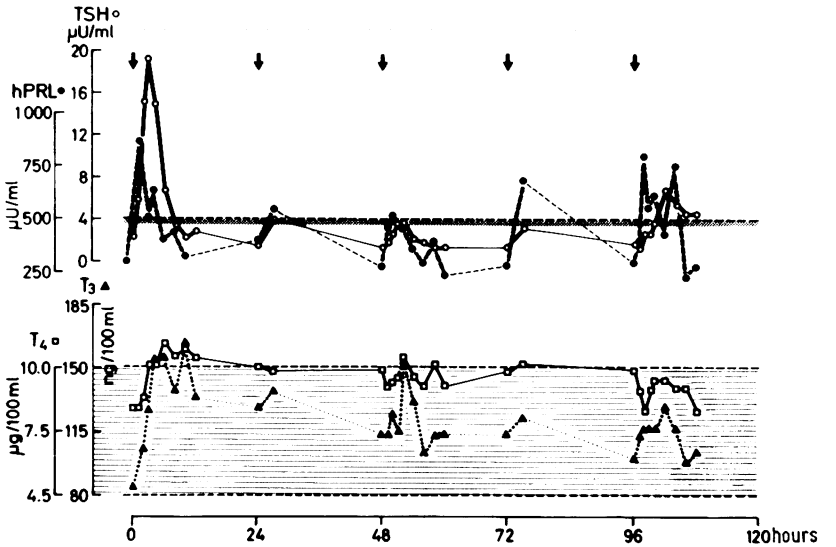

Fig. 3 Diminishing response of TSH and PRL secretion to repeated oral TRH administration (40 mg, arrows, cf. text, from Horn et al. [7, 8])

ance with its long half-life. Subsequent oral TRH applications led to much less pronounced increments in TSH. After four weeks of such a regimen (Table 3), the T_4 and T_3 levels remained practically normal, whereas the TSH response was blunted [8]. Apart from the physiological information obtained regarding the regulation of TSH secretion by thyroid hormones and TRH, respectively, this result provides a strong argument against any form of hypothalamic hyperthyroidism and against the "Schreck-Basedow" [7, 8].

Table 3 Effect of Oral TRH Application in Healthy Subjects (N = 12, 40 mg per day over a period of 4 weeks; from Horn et al. [8])

		before TRH	after TRH
Serum TSH (μU/ml)	basal	2.0 ± 0.8	1.0 ± 0.5*
	Δ TSH_{30min}	8.1 ± 3.0	3.0 ± 1.9*
Serum T_4 (μg/100ml)		6.2 ± 1.9	6.5 ± 1.8
Serum T_3 (ng/100ml)		112 ± 22	109 ± 32

* significance $p < 0.005$

Somatostatin

I am now turning briefly to the inhibitory hypothalamic hormones. Prolactin secretion appears to be the only example for a predomincance of the inhibitory factor, PIF. Somatostatin, originally discovered as the inhibiting factor of growth hormone secretion, apparently plays a most interesting role as local inhibitory factor for many secretory processes and may have additional functions as a neurotransmitter [6]. Three selected

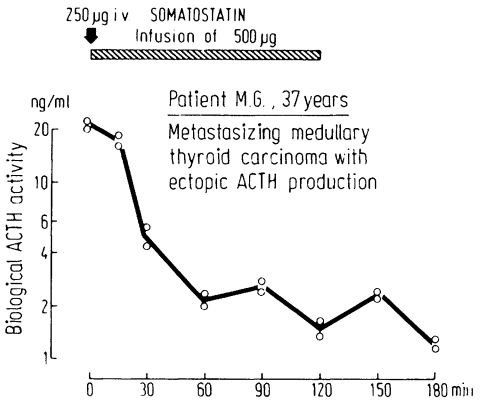

Fig. 4 Somatostatin inhibits ectopic ACTH secretion in a patient with calcitonin-producing medullary carcinoma of the thyroid and ectopic ACTH syndrome (from Müller et al. [13])

examples will be mentioned: first, the inhibition of ACTH secretion in Nelson's syndrome [24]; second, the same inhibition in 3 patients with Addison's disease [3]; and third, a patient, studied by Müller et al. [13], with a calcitonin-producing medullary carcinoma of the thyroid and an ectopic ACTH syndrome, where the ACTH levels could also be lowered by somatostatin (Fig. 4).

Unidentified pituitary Hormones?

Are there still unknown anterior pituitary hormones? This question arose during electronmicroscopic studies of Hachmeister [5] on pituitary adenomas operated on by Dr. Marguth and colleagues. In a number of hormonally inactive adenomas, i.e. from patients showing no hormonal excess according to the currently available radioimmunoassays, secretory granules were observed which did suggest some unidentified hormonal activity. Lipotropins might be a possiblility; unfortunately this question is far from being solved, since Dr. Schwandt's peptide B turned out to contain neurophysin, which itself is not lipolytic [14].

An interesting observation came from Boston recently. In a thorough study carried out on 60 patients with pituitary adenomas, Kourides et al. [9] observed 5 patients who showed an excess production of alpha-subunits, not explained by an excess of thyrotropin or gonadotropin. The field of unidentified secretory products of pituitary adenomas is obviously still open for new insights; these would be highly welcome in order to facilitate the handling of pituitary adenomas by monitoring through hormone determiations.

Antidiuretic Hormone

It is obvious that the discussion of neurohormones, of diabetes insipidus and of disorders of ADH secretion and thirst [20, 23] had to be excluded by the conveners. Just in order to remind the audience of the existence of these factors, I should like to mention the experiments of Gottsmann et al. [4, 25]. Here ADH secretion was a sensitive indicator of stress, as shown for 15 min kinetosis [25]. The increase and the peak in serum ADH were already observed at moderate severity of kinetosis [4] (Fig. 5). With respect to the impending Bavarian evening, it may be noteworthy that kinetosis is a more potent stimulus for ADH secretion than thirst.

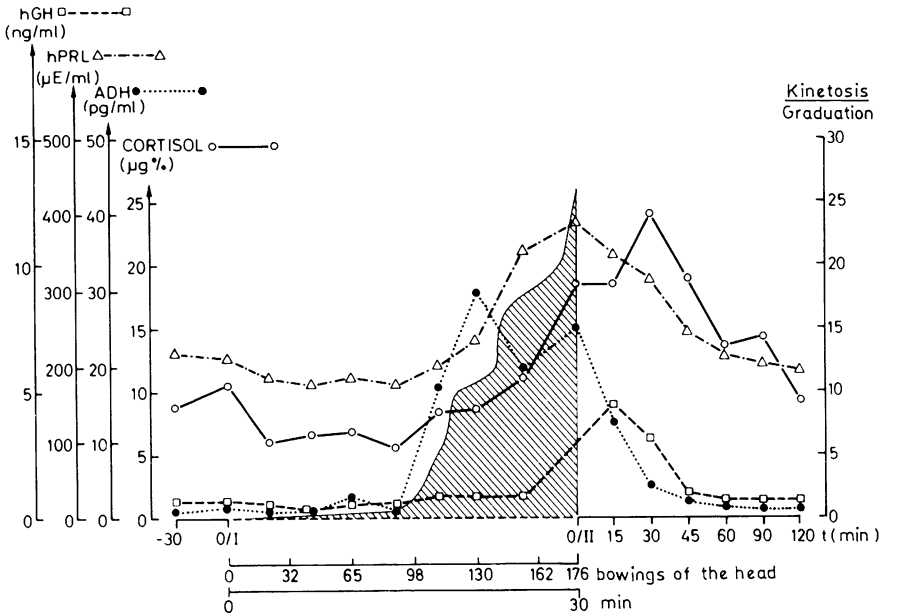

Fig. 5 Increase of serum ADH concentration as well as of other "stress hormones" during Coriolis stimulation. The hatched area represents the serverity of kinetosis, up to vomiting (from Gottsmann et al. [4])

Acknowledgments

This investigation was supported by the Deutsche Forschungsgemeinschaft (SFB 51)

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