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I. THE PERIPHERAL VISUAL PATHWAY

II. PITUITARY TUMORS

III. VARIA

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CONTENTS

III. VARIA

THE DIAGNOSTIC SIGNIFICANCE OF THE STIMULATION OF TSH SECRETION BY ADMINISTRATION OF THYROTROPIN RELEASING HORMONE (TRH) IN DISEASES OF THE HYPOTHALAMUS AND PITUITARY

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With the synthesis of the hypothalamic pituitary tropic hormone TRH (thyrotropin releasing hormone) (Bøler et al., 1969; Burgus et al., 1970; Folkers et al., 1970) and the development of TSH radioimmunoassay (Odell et al., 1965; Utiger, 1965; Erhardt et al., 1973) it is now possible for the first time to stimulate the pituitary-thyroid axis directly. The question may be asked whether the TRH stimulation test can help to differentiate between hypothyroidism of pituitary origin and that due to hypothalamic disturbance.

MATERIALS AND METHODS

Determination of serum TSH levels obtained in the TRH stimulation test and the assessment of thyroid function were carried out as described previously (Pickardt et al., 1972*a*). The 84 patients were divided into 6 groups after assessment of thyroid function and investigation of tumor expansion by radiological and ophthalmological techniques. These were patients with anterior pituitary adenomata, or with suprasellar expanding tumors, or with hypothalamic disease (Table I).

RESULTS

Twenty-five patients with hormonally inactive anterior *pituitary tumors* (Group I, Table I) were investigated preoperatively. Of these, 12 patients were euthyroid and had, as expected, normal stimulated TSH levels; 13 had *secondary hypothyroidism*; surprisingly, only one failed to show an increase in TSH secretion, while the remaining 12 had TSH increments in the normal range or above normal.

Twenty-three patients were investigated after operative treatment for hormonally inactive *anterior pituitary adenomata* (Group II, Table I). Three patients were euthyroid. Of these one already had a reduced TSH level after TRH stimulation and so might be expected to have later manifestations of secondary hypothyroidism. The 20 patients with *secondary hypothyroidism* were divided into 2 groups based on the behavior of their TSH levels. Eight of these *hypothyroid* patients had TSH levels which responded like those in Group I, while the remaining 12 displayed a lack of TSH increment after TRH stimulation. The findings showed that these patients had no anterior pituitary tissue that could be stimulated by TRH. Six hypothyroid patients, with one exception, had no residual thyrotropic function after treatment for tumors (Group III, Table I) with both intra- and suprasellar extension. Of the 11 patients with *suprasellar* disease (Group IV, Table I) 9 were hypothyroid. They all showed the expected rise of TSH secretion mediated by TRH, and in 3 cases this was higher than normal. The investigation of 18 patients (Groups V and VI, Table I) with hormone-secreting anterior pituitary adenomata, i.e. active acromegaly (13 cases), ACTH-producing tumors (4 cases) and 1 prolactin producing tumor, failed to indicate any parallel increase in secretion of TSH in ACTH-, prolactin- or growth hormone-producing tumors. Neither was there an inverse relationship between TSH and these hormones.

DISCUSSION

The results reported lead to 3 conclusions:
1. In patients with anterior pituitary adenomata secondary hypothyroidism is due to deficiency of TSH. However, this could be attributed in only a few cases to a complete lack of TSH-producing tissue. We found that hypothyroidism secondary to true pituitary failure occurred only after operative treatment of anterior pituitary tumors (Group II, Table I) and after treatment of tumors having both intra- and suprasellar extensions.

2. In patients with suprasellar disease the cause of the pituitary insufficiency must be due to a lack of the hypothalamic releasing hormone. As might be expected, therefore, administration of exogenous TRH produced an increase in TSH secretion in every case.

3. Rather surprisingly, in patients with anterior pituitary adenomata the *TSH levels* after TRH stimulation remained *normal* before operation (Group I, Table I) and in a few cases after operation (Group II, Table I) despite their having manifest *secondary hypothyroidism*. This finding, which is in contrast to the results of Hall et al. (1972), does not exclude an anterior pituitary tumor but it does prove the presence of TSH-producing tissue (Pickardt et al., 1972*b*). It must follow that the individual cause for secondary hypothyroidism is to be sought in the *suprapituitary area*. For this conclusion 2 hypothetical explanations are put forward. (At this point, it is perhaps important to mention that all but 2 patients had a *chiasma syndrome* as a consequence of suprasellar extension of their tumor.) One possible explanation was that by compression of the pituitary stalk the tumors caused a disturbance of

TABLE I

Results of stimulation of TSH levels in all investigated patients with pituitary tumors and hypothalamic disease

			No. of cases	Serum-TSH μU/ml, increment 30 min after TRH (normal range (log.): 2.73–23.6 μU/ml) Reduced	Normal	Raised
Group I						
Hormonally inactive		euthyroid	12		12	
ant. pituitary adenomata						
preoperative	(25 cases)	hypothyroid	13	1	**11**	**1**
Group II						
Hormonally inactive		euthyroid	3	**1**	2	
ant. pituitary adenomata						
postoperative	(23 cases)	hypothyroid	20	12	**6**	**2**
Group III						
Intra- and suprasellar		euthyroid	1	**1**		
tumors after treatment	(7 cases)	hypothyroid	6	5	**1**	
Group IV						
Suprasellar		euthyroid	2		2	
diseases	(11 cases)	hypothyroid	9		6	**3**
Group V						
Active acromegaly		euthyroid	9	1	4	**4**
	(13 cases)	sec. hypothyroid	2	1	**1**	
		prim. hypothyroid	2		**1**	1
Group VI						
Other hormonally active						
pituitary adenomata	(5 cases)	euthyroid	5	**3**	2	
		No. of investigations	84			

Bold numbers represent unexpected results.

circulation in the portal system, so preventing *endogenous* TRH from reaching the cells in the anterior pituitary. *Exogenous* TRH, however, could reach and stimulate the anterior lobe via the arterial system. This hypothesis proposes that there may be a mechanical occlusion of the portal system (Foley et al., 1972; Pickardt, 1972; Pickardt et al., 1972*b*) which acts as a suprapituitary cause for secondary hypothyroidism. The other explanation is that there may be a functional impairment of the hypothalamus itself with a lack by endogenous TRH. This could be looked for in patients with large expansion of their tumors. In such cases of anterior pituitary adenomata the cause of secondary hypothyroidism would lie in the hypothalamus. For the individual patient the true explanation will be arrived at only when measurement of TRH levels in serum becomes available.

SUMMARY

In the field of neurosurgery it would be useful to consider the following conclusions. In patients with anterior pituitary tumors a lack of TSH increment after TRH stimulation demonstrates an absence of thyrotropic anterior pituitary function. If one finds in patients with *secondary hypothyroidism* a TSH increment after TRH stimulation, one must conclude that there is *suprasellar extension* of the anterior pituitary tumor.

In addition to the neuroradiological and ophthalmological criteria there now exists an endocrinological method for the diagnosis of tumor expansion.

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