T3 receptors in human pituitary tumors

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Objective: *The purpose of this work was to investigate the synthesis of T3 receptors in human tumors of the anterior pituitary gland, its relationship with the hormone synthesized and/or secreted by the tumor and the post-surgical evolution of the patient.*
Methods: *Patients were evaluated clinically and by magnetic nuclear resonance to classify the adenoma according to their size. Hormonal concentrations in sera were determined by radioimmunoassay. Immunohistochemistry of the pituitary hormones was performed in the tumors. Tumors were obtained at surgery and immediately frozen in ice, transported to the laboratory and stored at −70°C. Reverse transcription was performed with purified RNA from the tumors.*
Results: *Out of 33 pituitary tumors, 29 had RNA for T3 receptors synthesis (88%). They were present in different histological specimens, the tumors were grades 1–4 according to their size, and there was no relationship between the size of the tumor and the presence of T3 receptor RNAs. The post-surgical evolution of the patient was mostly dependent on the size and not on the presence of T3 receptors.*
Discussion: *The presence of thyroid hormone receptors in pituitary tumors is in line with two important characteristics of these tumors: they are histologically benign and well differentiated.*
[Neurol Res 2009; **31**: 928–930]

Keywords: Pituitary tumors; receptor T3

INTRODUCTION

Thyroid hormone receptors (T3rs) are transcription factor members of a family of nuclear hormone receptors that also include the steroids, vitamin D and retinoic acid receptors[1]. There are two distinct T3r genes, α and β. The α generates two proteins, T3α1 and T3α2. The T3β generates isoforms 1 and 2 *via* a promoter's choice. Both proteins have an identical DNA and a ligand-binding domain but differ at their amino termini[2]. Although T3rs have widespread expression, T3rβ2 has a certain tissue-selective expression in the anterior pituitary gland (APG), hypothalamus and developing brain[2]. Thyroid hormone receptor beta 2 knockout mice have elevated serum thyrotropin (TSH) levels, suggesting that T3rβ2 negatively regulates TSH secretion. In a patient with a TSH-secreting pituitary tumor, there was T3rβ2 resistance because this protein was unable to bind with T3[1]. Patients with TSH-secreting pituitary tumors (TSHomas) have high serum TSH despite elevated thyroid hormone levels[1]. The regulation of thyroid hormone concentrations depends upon the interactions among thyroid hormones, hypothalamic TRH and pituitary TSH. The synthesis of T3r and TSH are negatively regulated by thyroid hormones. Because of the wide spectrum of actions of the thyroid hormones, T3r are rather ubiquitous in normal human tissues including the pituitary gland. The purpose of this work was to investigate the synthesis of T3r in human tumors of the APG (anterior pituitary gland), its relationship with the hormone synthesized and/or secreted by the tumor and the post-surgical evolution of the patient. We have previously demonstrated the presence of estrogen receptors in pituitary tumors mainly in prolactinomas and its presence as a sign of a better prognosis[4]. Most human pituitary tumors are histologically benign and well differentiated.

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MATERIAL AND METHODS

Patients were evaluated clinically and by magnetic nuclear resonance to classify the adenoma according to their size: between 1, which is a microadenoma, and 4 with extrasellar expansions. In our series, there were 12 macroadenomas (ten nonfunctioning, one acromegaly and one prolactinoma) and six microadenomas (five Cushing and one prolactinoma), and the other tumors were graded 2 or 3 (two nonfunctioning, nine acromegalies, one Cushing, one prolactinoma and two thyrotrophinomas). Hormonal concentrations in sera were determined by radioimmunoassay. Immunohistochemistry of the pituitary hormones was performed in the tumors to characterize them according to

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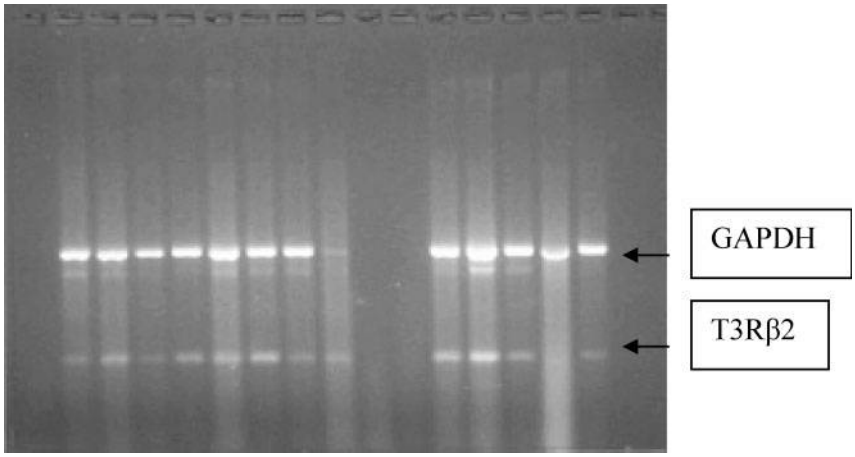

Figure 1: RT-PCR of T3Rβ2 and GAPDH in human pituitary tumors. These tumors where nonsecreting or secreting adrenocorticotrophic hormone, growth hormone, TSH and prolactin. Upper arrow, GAPDH; lower arrow, T3Rβ2

their main product of synthesis. With these parameters, there were six patients with Cushing disease, ten acromegalies, three prolactinomas, 12 nonsecreting and two thyrotrophinomas. Tumors were obtained at surgery and immediately frozen in dry ice, transported to the laboratory and stored at -70° later in RNA medium until processing of the tissue. Ribonucleic acid was purified according to the single-step method of Chomczynski and Sacchi[3]. Reverse transcription (RT) was performed with the enzyme MMLVTR and random primers followed by polymerase chain reaction (PCR) of T3rβ and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) products of the RT reaction and specific primers (*Figure 1*). The primers for T3rβ were forward primer 5′-GAAGACCAGATCATCCTCCTC-3′ and reverse primer 5′-GGAATTATGAGAATGAATCCAG-3′, and for GAPDH, forward primer 5′-GGGACGACA-TGGAGAAAA-3′ and reverse primer 5′-TTCATGAGG-TAGTCAGTCAGGT-3′ (Invitrogen, Carlsbad, CA, USA).

RESULTS

Because of the wide spectrum of actions of the thyroid hormones, the T3r is rather ubiquitous in human tissues including the pituitary gland. Out of 33 pituitary tumors (21 women and 12 men) studied, 29 (19 women and ten men) had RNA for T3r synthesis (88%). They were present in different histological specimens according to the main secreting hormone (*Table 1*).

RNA for T3r synthesis was not found in two Cushing and one prolactinoma (microadenomas) and one nonsecreting (macroadenoma).

Table 1: Number of patients

	Male +	Male −	Female +	Female −
Nonsecreting	3	1	8	0
Growth hormone	5	0	5	0
Adrenocorticotrophic	1	1	3	1
Tritrophic	0	0	2	0
Prolactin	1	0	1	1

The tumors were graded 1–4 according to their size, and we found no relationship between the size of the tumor and the presence of T3r RNAs. The post-surgical evolution of the patient was mostly dependent on the size. Thus, most of the grade 4 tumors had to be reoperated, and only one of the graded 1 required a second operation independently of T3r RNA.

DISCUSSION

We have previously shown that estrogen-binding sites in pituitary tumors are mainly present in prolactinomas and are important determinations to predict the post-surgical evolution of the patient with this pathology[4]. On the contrary, the presence of T3r appears as a more ubiquitous receptor, and it is present in 88% of the pituitary tumors. As in breast cancer, estrogen receptors appear as a sign of differentiation, and its presence predicts a better prognosis in pituitary adenomas. In this work, we have seen expression of T3r in most pituitary adenomas, whether small or large and whether they produce different pituitary hormones or not. After surgery, the patient's evolution was not related to T3r presence. The thyroid hormone T3 has multiple functions in the APG, such as the control of the thyroid axis, the secretion of growth hormone and the basal and estrogen-stimulated expression of anterior pituitary galanin[5]. The presence of T3rs in pituitary tumor may reflect that many of these functions are retained by the tumor cell, which is in line with two important characteristics of these tumors: they are histologically benign and well differentiated.

ACKNOWLEDGMENTS

This work was supported by the Universidad Abierta Interamericana and by the Consejo Nacional de Investigaciones Científicas y Tecnologicas.

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