Adult Plenary Session: Pituitary Tumorigenesis

HORMONE RESEARCH

Horm Res 2007;68(suppl 5):132–136
DOI: 10.1159/000110608

Published online: December 10, 2007

Targeting Pituitary Tumors

Anthony P. Heaney

Division of Endocrinology and Neurosurgery, David Geffen School of Medicine at UCLA, Los Angeles, Calif., USA

Key Words
Pituitary tumor · Tumorigenesis

Abstract
Background: Pituitary tumors are common and usually grow insidiously over many years. Rarely fatal, treatment still requires multiple cytoreductive surgeries and/or radiation therapy with its attendant side effects. As a disease process of regulatory pathways, pituitary tumors offer numerous potential therapeutic targets, and many, such as the membranal dopamine$_2$ and somatostatin receptors, have been successfully exploited for many years. Nuclear receptors, such as the estrogen receptor, peroxisome proliferator-activating receptor and retinoic acid receptor, are abundantly expressed in pituitary tumors, and a variety of increasingly potent and specific ligands are emerging. Subcellular therapies aimed at the pituitary tumor transforming gene may also have some utility in pituitary tumor management, though obstacles to targeting nuclear proteins using gene therapy still exist. Other novel agents such as doxazosin, an α-adrenoceptor blocker that appears to inhibit nuclear signaling mediated by nuclear factor kappa-B (NFκB), and epidermal growth factor receptor may also represent new and safe medical therapies for these benign but problematic tumors.
Conclusions: Increased understanding regarding the etiopathogenesis of pituitary tumors has identified new proteins and pathways that may lead to novel therapies. Empiric exploration of novel targeted therapies developed for other tumor types, guided by pharmacogenomic profiling studies, will likely reveal the utility of many of these novel targeted agents in the treatment of pituitary tumors.

Targeting Pituitary Tumors

Pituitary tumors occur following oncogene activation or tumor suppressor gene inactivation and are sustained by an environment rich in cytokines, angiogenic factors and growth factors [1]. Altered oncogenic Ras, Gsα mutations and increased pituitary tumor-derived transforming gene (*PTTG*/securin) expression or reduced tumor suppressor p21 or p16 expression have been described in pituitary tumors, but the extent of their contribution to pituitary tumorigenesis remains unclear [2]. Characterization of individual proteins or pathways key to tumor development and maintenance have now enabled targeting of differentially expressed elements critical to tumor survival and irreplaceable by alternative pathways, though targets fulfilling all criteria are scarce. The dopamine$_2$ receptor (D_2-R) in prolactinomas illustrates how successful a targeted therapy can be as D_2-R agonists, such as bromocriptine and cabergoline, effectively lower serum prolactin (PRL) levels and reduce pituitary tumor volume in the majority of patients with PRL-secreting tumors [3, 4]. D_2-agonist resistance in prolactinomas [5], though uncommon, may herald 'transformation' to inva-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0301–0163/07/6811–0132$23.50/0

Accessible online at:
www.karger.com/hre

Anthony P. Heaney, MD
Cedar-Sinai Medical Center, Endocrinology Metabolism
8700 Beverly Blvd, Plaza N, Becker B-131
Los Angeles, CA 90048 (USA)
Tel. +1 310 423 4774, Fax +1 310 423 0440, E-Mail aheaney@mednet.ucla.edu

sive prolactinomas – or rarely – carcinoma [6], requiring multiple pituitary debulking surgeries and radiation therapy.

We recently described a patient with a long-standing prolactinoma that became D_2-agonist resistant and locally metastasized to the cervical spine and cerebellopontine angle. Despite six surgical resections and maximal radiation therapy, tumors grew unabated and serum PRL level peaked at 7,093 ng/ml (fig. 1) [7]. However, serum PRL levels were reduced to near normal and the intrasellar and metastatic tumors exhibited a dramatic response after experimental therapy with temozolomide, an alkylating agent that avidly crosses the blood-brain barrier and is approved for treatment of refractory anaplastic astrocytoma [7, 8]. An additional report has demonstrated a response to temozolomide in a patient with pituitary carcinoma [9]. The increasing availability of oral cytotoxic agents with less severe side-effect profiles now warrants consideration of earlier, more aggressive management of highly invasive pituitary tumors with cytotoxic therapy, which may improve outcome.

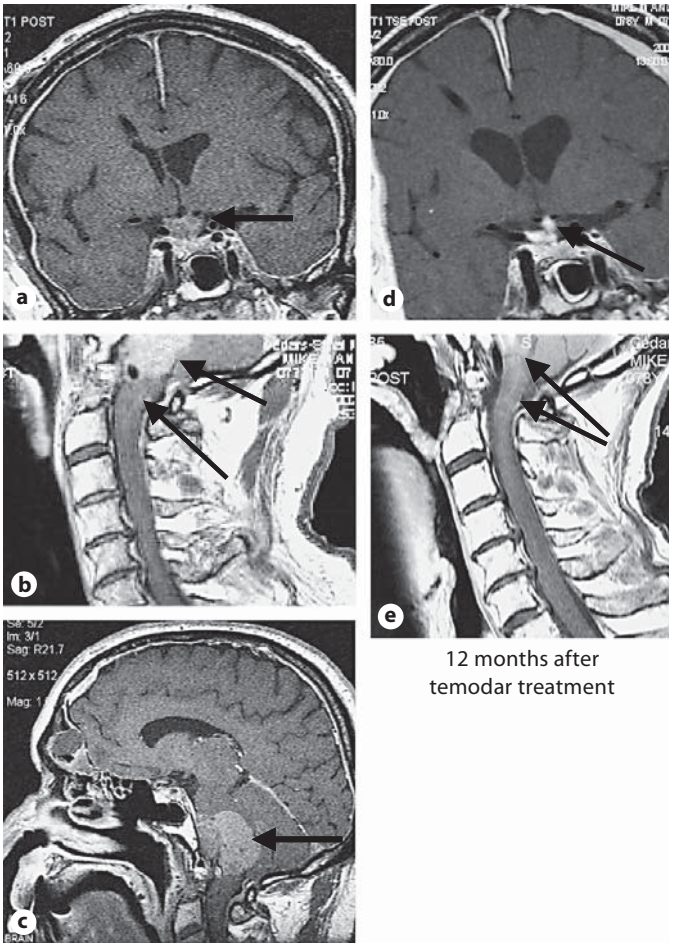

Fig. 1. Pituitary magnetic resonance scans depicting a large sellar pituitary tumor (**a**) and large cerebellopontine angle (**b** and **c**) and cervical metastatic deposits (arrow) despite six prior nearly total tumor resections and prior to initiation of temozolomide therapy. Twelve months after initiation of temozolomide therapy, both the sellar tumor mass and the metastatic deposits (**d** and **e**) have virtually disappeared.

PTTG/Securin

PTTG, a vertebrate securin isolated from rat pituitary tumor cells, regulates chromatid separation during mitosis [10, 11]. *PTTG1* exhibits a cell cycle-dependent expression pattern, increasing during S phase and peaking at the S-G_2 transition. A number of growth factors increase securin expression in animal models. In many of these models, however, it is unclear if PTTG induction occurred as a direct effect of the specific treatment agent or secondary to the associated proliferation-related activation of cell cycle proteins. Low-level *PTTG1* expression has been demonstrated in normal tissues including the pituitary, and increased *PTTG1* expression has been reported in numerous tumor types [12, 13]. In pituitary tumors, recent studies employing Western blot and immunocytochemistry have reported increased, mainly nuclear, PTTG immunoreactivity in ~90% of pituitary tumors tested and demonstrated the correlation between the presence of PTTG and proliferative markers such as Ki-67 [14].

Using murine models of *PTTG* knockout and overexpression, either alone or crossbred with heterozygous retinoblastoma-negative (Rb-deleted) mice, in vivo studies also point to a close correlation between PTTG content and proliferative status. For example, when heterozygous $Rb^{+/-}$ mice, which almost universally develop pituitary tumors, were crossbred with *Pttg1*-null mice, the transgenic $PTTG^{-/-}$ $Rb^{+/-}$ mice exhibited decreased cell proliferation rates and delayed pituitary tumor development [15]. In contrast, pituitary-directed transgenic *PTTG1* ok overexpression employing an α-subunit promoter resulted in pituitary focal hyperplasia of several cell subtypes, including growth hormone (GH), in addition to the anticipated transgene expression in luteinizing hormone (LH) and thyroid-stimulating hormone-secreting pituitary cells [16]. The pituitary morphological changes were supported by increased serum levels of LH, GH, testosterone and/or insulin-like growth factor-I. When these

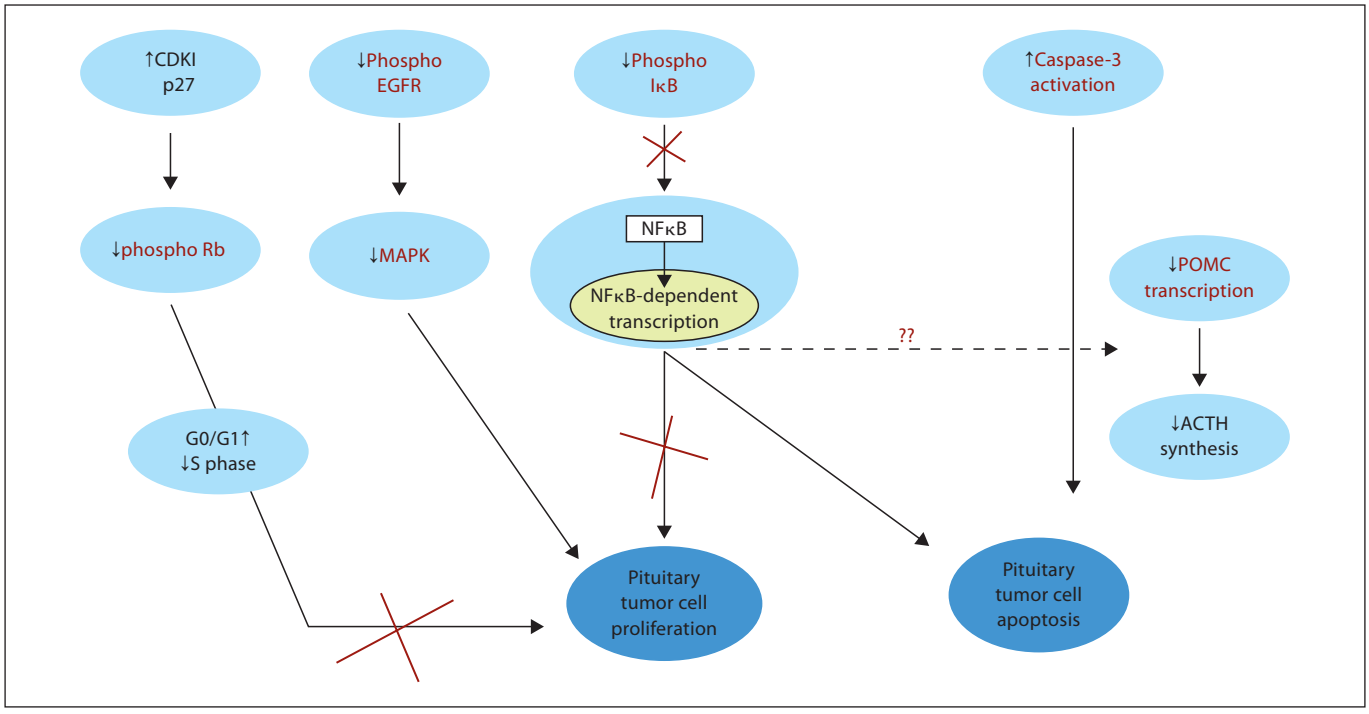

Fig. 2. Doxazosin exhibits multiple mechanisms of action to abrogate both endothelial growth factor receptor- and NFκB-mediated actions, thereby inhibiting tumor proliferation via reduced concentrations of cell-cycle proteins, p27 and pRb and by inducing apoptosis via caspase-3. CDKI = Cyclin-dependent kinase inhibitor; MAPK = mitogenic activating protein kinase; POMC = pro-opiomelanocortin; Rb = retinoblastoma.

αGSU-*PTTG1* mice were crossbred with $Rb^{+/-}$ mice, enlarged pituitaries were observed as early as 2 months of age, and anterior lobe tumors were increased compared with $Rb^{+/-}$ mice [17].

In summary, in vitro and in vivo studies now confirm that PTTG level correlates with proliferative state and tumor stage, but reverse transcription polymerase chain reaction and sequencing studies in various tumor types have not revealed mutations of the *PTTG1*-coding region or the *PTTG* promoter, and the cause of tumor *PTTG* overexpression has still not been entirely elucidated. Nonetheless, given its abundance in tumors, PTTG has emerged as a potential tumor target [18].

Estrogen Receptor as a Target in Pituitary Tumors

High-dose estrogen administration to transsexuals may augment growth of pituitary lactotroph tumors, ≤20% of macroprolactinomas enlarge during pregnancy and pituitary tumors, particularly prolactinomas, express the estrogen receptor [19, 20]. These findings suggest that estrogen receptors may serve as an effective target for treatment of pituitary tumors. Estrogen administration to Fisher-344 rats generated large PRL-secreting pituitary tumors in association with increased pituitary *PTTG/securin* mRNA levels, and pituitary *PTTG* expression correlated with the proestrus serum estradiol peak [21]. The antiestrogens raloxifene, tamoxifen and ICI 182780 blocked estrogen-induced pituitary *PTTG* expression and significantly inhibited lactotroph growth in tumor-bearing mice [22]. Antiestrogen treatment reduced *PTTG* expression in human pituitary tumor cultures in vitro [22] and, though experience with antiestrogen treatment in human pituitary tumors is limited, these studies raise the possibility that antiestrogen treatment may offer therapeutic efficacy in some pituitary tumors.

Retinoic Acid and PPARγ Ligands

Following ligand binding, the nuclear receptors peroxisome proliferator-activated receptor γ (PPARγ) and retinoic acid receptor (RAR) α, β, γ form a homodimer-

ic complex or heterodimerize with retinoic-X receptor (RXR) to release corepressors and recruit transcriptional coactivators to regulate a diverse range of genes involved in transcription, apoptosis and proliferation. Natural RAR and PPARγ ligands include the retinoids, eicosanoids and fatty acids, respectively, and several synthetic vitamin A derivatives and high-affinity thiazolidinedione compound (TZD) PPARγ ligands have been developed. At pharmacological dosages, retinoids and synthetic PPARγ ligands inhibit tumor cell growth, and in clinical trials retinoids have shown efficacy for treatment of acute promyelocytic leukemia and skin and cervical squamous carcinoma [23]. A recent study has also demonstrated the efficacy of retinoic acid in canine models of Cushing disease [24]. Unfortunately, the retinoid concentrations required for anticancer actions also cause deranged liver function, conjunctivitis, mucositis and severe photosensitivity. Recent studies have demonstrated increased pituitary tumor PPARγ expression, inhibition of pituitary tumor proliferation and increased pituitary tumor apoptosis in vitro following TZD treatment [25, 26]. Additionally, in vivo rosiglitazone treatment inhibited pituitary tumor growth in mice and reduced pituitary tumor-derived hormone levels, and limited clinical studies have suggested that rosiglitazone may also lower plasma adrenocorticotropic hormone and cortisol levels in ~40% of patients with Cushing disease [25–27]. More recent therapeutic approaches have demonstrated synergistic growth-inhibitory actions of RAR, RXR and PPARγ ligands. Potentially, combination therapy with an RXR and the PPARγ ligand would reduce retinoid toxicity by allowing the use of lower concentrations of retinoids, thereby providing a potential novel pituitary tumor therapy.

Quinazoline-Based α-Adrenergic Receptor Antagonists

Doxazosin is one of several quinazoline-based, α-adrenergic receptor antagonists developed to treat hypertension and obstructive uropathy [28]. Doxazosin-mediated antiproliferative effects have been described in prostate tumors, where increased prostate cancer cell apoptosis and decreased serum prostate-specific antigen levels were reported in patients with prostate cancer. Treatment of murine pituitary tumor corticotroph (AtT20) and gonadotroph ($L\beta T_2$, and αT_3) tumor cells with doxazosin 10–30 μM in vitro inhibited cell proliferation, increased apoptosis and slowed in vivo tumor development [29]. However, α_1-adrenergic receptor expression was not detectable in several of the pituitary tumor cell lines, and cotreatment of the pituitary tumor cells with the noncompetitive α-adrenoreceptor blocker phenoxy benzamine and doxazosin together did not abrogate doxazosin-mediated apoptosis. This suggested that the antiproliferative and proapoptotic actions of doxazosin were not entirely mediated via the α adrenoreceptor. Additional studies demonstrated that doxazosin treatment reduced levels of phosphorylated inhibitor of κB inhibitor kinase to inhibit the NFκB-mediated regulation of a number of target genes including pro-opiomelanocortin [29]. In studies in breast cancer cells, doxazosin exhibited tyrosine kinase-like activity, reduced phosphorylated epidermal growth factor receptor levels and inhibited mitogen-activated protein kinase-mediated signaling [30]. These findings indicate that doxazosin acts on multiple targets in pituitary and other tumors. Given its established safety profile, doxazosin may represent an attractive, safe option for pituitary tumor therapy.

Conclusions

Pituitary tumors offer numerous potential therapeutic targets. Their slow growth permits multiple therapeutic strategies and may limit the development of drug resistance, which is likely to be a problem in some more aggressive tumor types. Empiric exploration of novel targeted therapies developed for other tumor types, guided by pharmacogenomic profiling studies, will likely reveal the utility of many of these novel targeted agents in the treatment of pituitary tumors.

Acknowledgments

Work in the author's laboratory is supported by grants from the National Institutes of Health (CA 114714) and the Division of Neurosurgery, UCLA School of Medicine.

Disclosure Statement

The author has a relevant financial relationship with a commercial interest. He is a speaker/teacher at Novartis and a member of the Advisory Board of Novartis. Honoraria have been received from Pfizer. The presentation includes discussion of investigational or unlabeled uses of products.

References

1 Heaney AP, Melmed S: Molecular targets in pituitary tumors. Nat Rev Cancer 2004;4:285–294.
2 Heaney AP: Pituitary tumor pathogenesis. Br Med Bull 2006;75:81–97.
3 Freda PU, Wardlaw SL: Diagnosis and treatment of pituitary tumors. Clinical Review 110. J Clin Endocrinol Metab 1999;84:3859–3866.
4 Colao A, Di Sarno A, Cappabianca P, Di Somma C, Pivonello R, Lombardi G: Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. N Engl J Med 2003;349:2023–2033.
5 Caccavelli L, Morange-Ramos I, Kordon C, Jaquet P, Enjalbert A: Alteration of Gα subunits mRNA levels in bromocriptine resistant prolactinomas. J Neuroendocrinol 1996;8:737–746.
6 Delgrange E, Sassolas G, Perrin G, Jan M, Trouillas J: Clinical and histological correlations in prolactinomas, with special reference to bromocriptine resistance. Acta Neurochir (Wien) 2005;147:751–758.
7 Lim S, Shahinian H, Hakimian B, Maya M, Yong W, Heaney AP: Temodar: novel treatment for pituitary carcinoma. Lancet Oncol 2006;7:518–520.
8 Mason WP, Cairncross JG: Drug insight: temozolomide as a treatment for malignant glioma – impact of a recent trial. Nat Clin Pract Neurol 2005;1:88–95.
9 Kovacs K, Horvath E, Syro LV, Uribe H, Penagos LC, Ortiz LD, Fadul CE: Temozolomide therapy in a man with an aggressive prolactin-secreting pituitary neoplasm: morphological findings. Hum Pathol 2007;38:185–189.
10 Pei L, Melmed S: Isolation and characterization of a pituitary tumor transforming gene (PTTG). Mol Endocrinol 1997;11:433–441.
11 Zou H, McGarry TJ, Bernal T, Kirschner MW: Identification of a vertebrate sister-chromatid separation inhibitor involved in transformation and tumorigenesis. Science 1999;285:418–422.
12 Heaney AP, Singson R, McCabe CJ, Nelson V, Nakashima M, Melmed S: Expression of pituitary-tumour transforming gene in colorectal tumours. Lancet 2000;355:716–719.
13 McCabe CJ, Khaira JS, Boelaert K, Heaney AP, Tannahill LA, Hussain S, Mitchell R, Olliff J, Sheppard MC, Franklyn JA, Gittoes NJ: Expression of pituitary tumour transforming gene (PTTG) and fibroblast growth factor-2 (FGF 2) in human pituitary adenomas: relationships to clinical tumour behaviour. Clin Endocrinol (Oxf) 2003;58:141–150.
14 Filipella M, Galland F, Kujas M, Young J, Faggiano A, Lombardi G, Colao A, Meduri G, Chanson P: Pituitary tumor transforming gene (PTTG) expression correlates with the proliferative activity and recurrence status of pituitary adenomas: a clinical and immunohistochemical study. Clin Endocrinol (Oxf) 2006;65:536–543.
15 Chesnokova V, Kovacs K, Castro AV, Zonis S, Melmed S: Pituitary hypoplasia in Pttg–/– mice is protective for Rb+/– pituitary tumorigenesis. Mol Endocrinol 2005;19:2371–2379.
16 Abbud RA, Takumi I, Barker EM, Ren SG, Chen DY, Wawrowsky K, Melmed S: Early multipotential pituitary focal hyperplasia in the α-subunit of glycoprotein hormone-driven pituitary tumor-transforming gene transgenic mice. Mol Endocrinol 2005;19:1383–1391.
17 Donangelo I, Gutman S, Horvath E, Kovacs K, Wawrowsky K, Mount M, Melmed S: PTTG over-expression facilitates pituitary tumor development. Endocrinology 2006;147:4781–4791.
18 Horwitz GA, Miklovsky I, Heaney AP, Ren S-G, Melmed S: Human pituitary tumor transforming gene (PTTG1) motif represses prolactin expression. Mol Endocrinol 2003;17:600–609.
19 Molitch ME: Management of prolactinomas during pregnancy. J Reprod Med 1999;44:1121–1126.
20 Kovacs K, Stefeaneau L, Ezzat S, Smyth HS: Prolactin-producing pituitary adenoma in a male-to-female transsexual patient with protracted estrogen administration. A morphologic study. Arch Pathol Lab Med 1994;118:562–565.
21 Heaney AP, Horwitz GA, Wang Z, Singson R, Melmed S: Early involvement of estrogen-induced pituitary tumor transforming gene (PTTG) and fibroblast growth factor expression in prolactinoma pathogenesis. Nat Med 1999;5:1317–1321.
22 Heaney AP, Fernando M, Melmed S: Functional role of estrogen in pituitary tumorigenesis. J Clin Invest 2002;109:277–283.
23 Kuri JM: The biologic basis for the use of retinoids in cancer prevention and treatment. Curr Opin Oncol 1999;11:497–502.
24 Castillo V, Giacomini D, Paez-Pereda M, Stalla J, Labeur M, Theodoropoulou M, Holsboer F, Grossman AB, Stalla GK, Arzt E: Retinoic acid as a novel medical therapy for Cushing's disease in dogs. Endocrinology 2006;147:4438–4444.
25 Heaney AP, Fernando M, Yong W, Melmed S: Functional PPAR-γ receptor represents a novel therapeutic target in Cushing's disease. Nat Med 2002;11:1281–1287.
26 Bogazzi F, Ultimeri F, Raggi F, Russo D, Vanacore R, Guida C, Viacava P, Cecchetti D, Acerbi G, Brogioni S, Cosci C, Gasperi M, Bartalena L, Martino E: PPARgamma inhibits GH synthesis and secretion and increases apoptosis of pituitary GH-secreting adenomas. Eur J Endocrinol 2004;150:863–875.
27 Ambrosi B, Dall'Asta C, Cannavo S, Libe R, Vigo T, Epaminonda P, Chiodini I, Ferrero S, Trimarchi F, Arosio M, Beck-Pecoz P: Effects of chronic administration of PPAR-γ receptor ligand rosiglitazone in Cushing's disease. Eur J Endocrinol 2004;151:1–7.
28 Kyprianou N, Benning C: Suppression of human prostate cancer cell growth by α1-adrenoceptor antagonist doxazosin and terazosin via induction of apoptosis. Cancer Res 2000;60:4550–4555.
29 Fernando M, Heaney AP: Alpha adrenergic antagonists: novel therapy for pituitary adenomas. Mol Endocrinol 2005;19:3085–3096.
30 Hui H, Fernando MA, Heaney AP: The α1-adrenergic receptor antagonist doxazosin inhibits EGFR and NF-κB signaling to induce breast cancer cell apoptosis. Eur J Cancer 2007 (in press).