CLINICAL STUDY

The relationship between pituitary tumour transforming gene (PTTG) expression and in vitro hormone and vascular endothelial growth factor (VEGF) secretion from human pituitary adenomas

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Abstract

Objective: Pituitary tumour transforming gene (PTTG) is a recently identified protooncogene, ubiquitously expressed in pituitary tumours at levels higher than those detected in normal pituitary. Although the precise function of PTTG protein is unknown, in vitro experiments have shown that it induces angiogenesis. In this study, we have examined the potential relationship between the level of PTTG expression and tumour phenotype, tumour size, in vitro pituitary hormone secretion and release of vascular endothelial growth factor (VEGF), a potent angiogenic factor.

Methods: Pituitary tumours (12 somatotroph, five lactotroph, five corticotroph and 18 non-functioning) were studied by cell culture, measuring the basal secretion of anterior pituitary hormones and VEGF in vitro. Immunocytochemistry was used to confirm the clinical diagnosis and tumour phenotype. PTTG mRNA expression was investigated by comparative RT-PCR. Tumour volume was quantitated from pre-operative MRI scans.

Results: PTTG expression was significantly increased 2.7-fold in somatotroph tumours compared with non-functioning adenomas (P < 0.01, ANOVA). A positive correlation was demonstrated between PTTG expression and in vitro GH secretion (r = 0.41, P < 0.01, Spearman) but no correlations were found for any of the other pituitary hormones. In 16 out of 40 pituitary tumours, we were able to determine the in vitro secretion of VEGF and relate this to PTTG expression. All of the adenomas tested secreted measurable VEGF but there was no correlation between the amount of VEGF secreted and either the tumour phenotype or PTTG expression. Neither PTTG expression nor VEGF secretion correlated with tumour volume.

Conclusions: Our studies have confirmed the presence of PTTG in pituitary adenomas and demonstrated a higher level of expression in somatotroph tumours and a significant correlation with GH secretion. We failed to demonstrate a relationship between PTTG expression and production of the angiogenic factor, VEGF, or tumour volume. Thus, although PTTG induces angiogenesis experimentally, it seems unlikely that a VEGF-mediated angiogenic mechanism occurs during pituitary tumour progression.

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Introduction

The molecular mechanisms involved in the aetiology of pituitary adenomas remain to a large extent obscure. The recent isolation of pituitary tumour transforming gene (PTTG) from rat growth hormone (GH) and prolactin (PRL) secreting cells (1) has provoked considerable interest in the role of this novel oncogene in pituitary tumour pathogenesis. Over-expression of PTTG leads to cell transformation in vitro and induces tumour development in athymic nude mice (1). PTTG has been cloned from human tissue (2) and the human PTTG family is now known to consist of at least three genes (PTTG1, PTTG2 and PTTG3), each located on different chromosomes (3). PTTG1 is expressed at high levels in various human tumours, including tumours of the pituitary gland, adrenal gland, kidney, endometrium, uterus and ovary, and in cell lines derived from various tumours (2, 4, 5). With the exception of the testis and the thymus, levels of PTTG1 mRNA are either low or undetectable in normal adult human tissues (2). The hPTTG2 gene
is expressed in most normal and tumour tissues, while the hPTTG3 gene is expressed only in ovarian tumour and ovarian tumour cell lines (3). These results suggest tissue-specific expression of all three PTTG genes and imply differential roles for them in normal cellular function and tumourigenesis.

Although the precise function of PTTG protein is unknown, the presence of specific structural motifs has suggested that it functions as a securin protein, with its over-expression leading to dysregulated sister chromatid separation and aneuploidy (6). Other evidence suggests that PTTG may function to induce cell transformation by inducing angiogenesis and stimulating production of angiogenic growth factors such as basic fibroblast growth factor (bFGF) (2, 7). Angiogenesis is regarded as an essential step in the formation of solid tumours, although it is not yet known whether angiogenic factors are implicated in the development and progression of pituitary tumours. Abnormal expression of bFGF (8) and its receptor isoforms (9) has been reported in pituitary tumours and bFGF also stimulates PRL secretion in vitro (10). Interestingly, a recent report has suggested that both rodent and human pituitary tumour cells are capable of producing the potent angiogenic factor, vascular endothelial growth factor (VEGF) (11), and VEGF protein expression in human pituitary adenomas has been demonstrated by immunocytochemistry and in situ hybridisation (12). One study has reported that levels of VEGF mRNA are strongly correlated with PTTG and bFGF mRNA expression in sporadic pituitary tumours (13) and in vitro expression of PTTG in some human non-pituitary tumour cell lines has been reported recently to stimulate VEGF mRNA (14).

Increased expression of PTTG has been demonstrated in sporadic pituitary adenomas compared with normal pituitaries, with the highest expression observed in hormone-secreting pituitary tumours that had invaded the sphenoid bone (15). However, in no study has PTTG expression been correlated with in vitro data on hormone secretion. We have therefore examined PTTG expression in a series of pituitary tumours and correlated the expression with tumour size and in vitro hormone and VEGF release from cultured pituitary tumour cells.

Subject and methods

Clinical details and patient selection

Pituitary tumours were collected from patients at the time of transphenoidal adenomectomy. Tissues were divided at the time of surgery for diagnostic histological studies and for tissue culture. All subjects gave informed consent, at the time of operation, for surgical specimens to be used for diagnostic and research purposes.

Acromegaly was diagnosed in patients with typical clinical features and persistently measurable GH with inadequate suppression on administration of an oral glucose load. Patients with corticotroph adenomas presented with typical clinical and biochemical features of cortisol excess. A pituitary source of adrenocorticotrophin (ACTH) hypersecretion was confirmed by inferior petrosal venous sampling. Patients who presented due to mass effect, without clinical features of pituitary hormone secretion, and with luteinising hormone/follicle-stimulating hormone (LH/FSH) levels inappropriately low for the level of their gonadal steroids were classified as clinically non-functioning pituitary adenomas (NFPAs). The diagnosis of PRL-secreting macroadenoma was on the basis of clinical features of PRL hypersecretion with raised serum PRL above 2000 mU/l that was incompletely suppressed to below the hormone assay detection limit by low-dose dopamine agonist therapy. All clinical prolactinomas subsequently had the diagnosis confirmed following tumour removal and stained strongly positive on immunostaining with PRL antibody. After surgery, all tumours were classified according to their morphological and immunocytochemical characteristics by light microscopy. Tumours were excluded from the series if microscopy suggested an alternative histological diagnosis, if significant normal pituitary tissue was present on microscopy, or if the tissue appeared necrotic. Tumour volume was determined from pre-operative magnetic resonance imaging (MRI) using previously validated methods (16).

Morphology and immunocytochemistry

All tumours were examined by standard haematoxylin and eosin, reticulin, and periodic acid–Schiff stains, and routine immunostaining was performed for GH, PRL, ACTH, thyrotrophin (TSH), LH, FSH (antibodies against the whole molecule obtained from BioGenex Laboratories, Inc., Berks, UK) and alpha subunit (a-SU) (rabbit polyclonal, UCB Bioproducts, Braine-L’Alleud, Belgium) using a standard streptavidin–biotin–horseradish peroxidase method. The amount of staining was assessed semi-quantitatively and reported as positive when 10–50% of cells were stained. The distinction between normal pituitary gland and tumour was confirmed by reticulin staining in all cases.

Pituitary tumour cell culture

Pituitary adenoma tissue was transported to the laboratory in DMEM containing 10% (vol/vol) heat-inactivated FCS, 0.06 g/l penicillin, 0.1 g/l streptomycin and 2.5 g/l fungizone (Life Technologies, Inc., Paisley, UK) hereafter referred to as culture medium. Tumour tissue was dispersed enzymatically with trypsin as described previously (17). Dispersed cells were harvested by centrifugation, washed once, and

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subsequently resuspended in culture medium. Cell viability was assessed using trypan blue exclusion and was more than 90% in all of the tumours studied after cell dispersion. Cell yield from each tumour varied from 1.0 to 15.0 x 10⁶ cells. The cells were plated in six-well plates at approximately 1 x 10⁶ cells/well in 3 ml medium. Cultures were incubated at 37°C in a humidified atmosphere of 95% air and 5% CO₂ for 48 h to allow cell attachment to occur, after which time the medium was collected and assayed for basal hormone secretion as described below. Adherent cells were lysed with a buffered guanidinium thiocyanate solution and stored at −70°C before mRNA extraction (see below).

mRNA analysis

Cell extract from cultured cells was thawed on ice and centrifuged to remove cell debris. mRNA was extracted according to a standard technique (Pharmacia Biotech, Uppsala, Sweden) using oligo(dexoxythymidine)-cellulose and washed first with 0.5 mol/l NaCl (high salt) and then with 0.1 mol/l NaCl (low salt), each containing 10 mmol/l Tris–HCl (pH 7.5) and buffered with 1 mmol/l ethylenediamine tetraacetate. Bound polyadenylated RNA was further washed with low salt buffer in a MicroSpin column (Pharmacia Biotech) and then eluted in 10 mmol/l Tris–HCl (pH 7.5) with 1 mmol/l ethylenediamine tetraacetate. mRNA was recovered by precipitation with glycogen (0.25 g/l) and 0.25 mol/l potassium acetate (pH 5.0) followed by centrifugation before mRNA extraction was verified in each reaction by PCR or GAPDH subsequently. The integrity of RNA from each specimen was verified in each reaction by PCR using GAPDH primers (Table 1).

The size of the predicted product was visualised by 1.6% agarose gel electrophoresis with ethidium bromide staining. By performing serial dilutions of a known quantity of starting mRNA, it was possible to determine that there was a linear relationship between starting mRNA and the optical density of the PCR band generated. Confirmation of hPTTG products was performed by direct automated DNA sequencing.

Assays for pituitary hormones, VEGF and S100 protein

GH, PRL, LH, FSH and TSH were measured using two-site chemiluminescent enzyme immunometric assays on the Immulite auto-analysers (Euro/DPC Ltd, Gwynedd, UK). The intra- and interassay coefficients of variation for all of these assays are less than 6% and 10% respectively. ACTH was measured by a specific double antibody RIA (Euro/DPC Ltd) with intra- and inter-assay coefficients of variation of less than 10%. α-SU concentrations were measured by a direct double antibody RIA using antibodies purchased from UCB Bioproducts (Brussels, Belgium) and chloramine-T-iodinated antigen (National Institute for Biological Standards and Controls reagent 76/508, Potters Bar, UK) and were calibrated against the First International Reference Preparation 75/569 (National Institute for Biological Standards and Controls). Intra- and interassay coefficients of variation were less than 6% and less than 11% respectively. Cross-reactivities (nanograms per nanogram) with purified LH, FSH and TSH were 3.6%, 1.9% and 1.3% respectively.

Table 1 Description of primers used and PCR conditions.

<table>
<thead>
<tr>
<th>Primer sequence</th>
<th>Nucleotide</th>
<th>Fragment length</th>
<th>Annealing temperature (°C)</th>
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<tbody>
<tr>
<td>PTTG</td>
<td>254–274</td>
<td>204</td>
<td>55</td>
</tr>
<tr>
<td>GAPDH</td>
<td>276–293</td>
<td>762</td>
<td>55</td>
</tr>
</tbody>
</table>

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VEGF was measured using a specific two-site enzyme immunometric assay (Quantikine, R&D Systems, Oxon, UK) with inter- and intra-assay coefficients of variation of less than 8%. The folliculostellate cell marker, S100 protein, was measured using an immunoluminometric assay (LIA-mat Sangtec 100, Cambridge Life Sciences, Cambs, UK) with intra- and inter-assay coefficients of variation of less than 6%. The detection limits of the above assays, defined as the concentration 2 s.d. above the response at zero dose, were as follows: GH, 0.5 mU/l; PRL, 10 mU/l; LH, 0.4 IU/l; FSH, 0.6 IU/l; TSH, 0.008 mU/l; ACTH, 4 pmol/l; α-SU, 0.1 μg/l; VEGF, 5.0 ng/l and S100, 0.1 μg/l. All samples from each individual tumour were analysed in the same assay. Hormone, VEGF and S100 data were initially obtained as concentrations, but were then corrected for cell number and incubation time. The data presented are therefore expressed as the amount secreted per 10⁶ cells per 24 h. The reported detection limits were as follows: GH, 2.0 μU; PRL, 50 μU; LH, 2.0 mIU; FSH, 3.0 mIU; TSH, 0.1 μU; ACTH, 20 fmol; α-SU, 0.5 ng; VEGF, 7.0 pg and S100, 0.5 ng.

Statistical analysis

All statistical analysis was performed using GraphPad Prism software (Graphpad Software Inc., San Diego, CA, USA). Data from in vitro hormone secretion did not conform to a normal distribution, and was not amenable to transformation given a high proportion of data points that fell below a detection threshold. Non-parametric analysis was therefore used throughout. Spearman rank correlation coefficients (r) were calculated to examine the correlations between the secretion of each hormone or VEGF and PTTG expression. Statistical analysis of PTTG expression between tumour types was performed using ANOVA followed by Tukey's multiple comparison. All data are expressed as means±S.E.M. For all tests, P < 0.05 was considered statistically significant.

Results

We examined PTTG expression in tumour tissue from 40 patients. These tumours were rigorously classified on clinical and histological criteria and in vitro hormone secretion (Table 2). Pituitary tumours comprised 12 somatotroph, five corticotroph, five lactotroph and 18 non-functioning adenomas. Figure 1 shows the PCR products generated using PTTG and GAPDH primers from a representative selection of tumours. PTTG PCR products were subsequently gel extracted and sequenced, in each case confirming the GenBank cDNA sequences. PTTG expression was present in all tumours tested regardless of tumour phenotype. When PTTG expression was expressed relative to the housekeeping gene GAPDH (Table 2, last column and Fig. 2) differences in the level of expression between tumours was apparent.

PTTG expression was significantly increased 2.7-fold in somatotroph tumours (PTTG : GAPDH = 0.91±0.16), compared with non-functioning adenomas (PTTG : GAPDH = 0.34±0.07; P < 0.01; Fig. 2). Mean PTTG expression in somatotroph tumours was also higher than in corticotroph and lactotroph tumours, though statistical comparison of the values failed to reach significance, possibly due to the small numbers in these two groups.

Spearman rank correlation coefficients were calculated to determine any interrelationships between the in vitro secretion of pituitary hormones (including α-SU) and PTTG expression (Table 3). A significant and positive correlation was demonstrated between GH secretion and PTTG expression, but no significant correlations were observed for any of the other hormones or α-SU. Thus, the highest level of PTTG expression was observed in somatotroph tumours and expression was correlated with in vitro GH secretion.

In 16 pituitary tumours (nine non-functioning, two corticotroph, four somatotroph and one lactotroph adenoma) we were able to determine the in vitro secretion of VEGF and relate this to the expression of PTTG mRNA. All of the human pituitary adenomas tested secreted measurable VEGF (range: 7.9–130.0 pg/10⁶ cells per 24 h) but there was no significant difference between the amount of VEGF secreted and the tumour phenotype (data not shown). There was no significant correlation between VEGF secretion and PTTG expression in the tumours studied (Fig. 3), nor was a significant correlation between VEGF and in vitro secretion of any other hormone demonstrated (data not shown).

Tumour volume was calculated from pre-operative MRI studies and compared with PTTG expression in 19 pituitary tumours (nine non-functioning, seven somatotroph, two lactotroph and one corticotroph adenoma) and VEGF secretion in ten pituitary tumours (five non-functioning, three somatotroph, one lactotroph and one corticotroph adenoma) (Fig. 4). No correlation was found between tumour volume and PTTG mRNA level (Fig. 4a) (r = 0.108, P = NS) or VEGF secretion (Fig. 4b) (r = −0.248, P = NS) in the tumours studied.

Although VEGF immunoreactivity is reported as present in human pituitary adenomas (12), it is not clear from which cell type VEGF is produced and in non-tumorous human pituitary, VEGF immunoreactivity co-localises mainly with somatotrophs and folliculostellate cells (19). In 10 out of 16 of the adenomas in which VEGF secretion was measured, sufficient media was available to measure S100 protein, a folliculostellate-specific marker (20). In the majority of these ten tumours, levels of S100 protein were low (<2.5 ng/10⁶ cells per 24 h) but the two tumours with high levels of S100 protein also had the highest
levels of VEGF secretion. A significant correlation was obtained ($P < 0.05$, $r = 0.78$) between VEGF and S100 secretion in the ten tumours studied (Fig. 5), suggesting that VEGF may be released from folliculo-stellate cells in the culture rather than the pituitary adenoma cells.

**Discussion**

Previous studies using comparative RT-PCR have demonstrated ubiquitous expression of PTTG in human pituitary adenomas with the level of expression being greater than that observed in normal pituitary (15). In this study, we have examined a large series of pituitary tumours for the presence of PTTG and related expression to tumour type, tumour size and in vitro secretion of pituitary hormones and VEGF.

PTTG expression was present in each of the 40 tumours studied but with apparent differences in the relative level of expression between tumour types. Somatotroph tumours showed a 2.7-fold increase in PTTG mRNA expression compared with non-functioning...
adenomas. This is perhaps not surprising given that PTTG was first isolated from GH-secreting pituitary cell lines (1). One other report has suggested that PTTG shows pituitary tumour sub-type specific expression with differences in the levels of expression between non-functioning and functioning tumours (21), although this report made no distinction among the different functioning tumour subtypes.

No previous studies have related PTTG expression to levels of hormones secreted in vitro. Our study demonstrated a significant positive correlation between in vitro GH secretion and the relative level of PTTG expression, again suggesting a role for PTTG in somatotroph-derived adenomas. This correlation between PTTG expression and GH secretion in all pituitary tumours studied suggests that there may be a specific effect of PTTG on GH transcription in pituitary adenomas. A role for PTTG as a transcriptional activator has been suggested in recent studies where it has been shown to increase transcription of bFGF (22) and the c-myc oncogene (23). It remains to be established whether PTTG expression induces transcriptional

**Table 3** Correlation between PTTG expression and *in vitro* hormone secretion from all tumour types (*n* = 40).

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Correlation coefficients (r) (PTTG vs hormone levels)</th>
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<tbody>
<tr>
<td>GH</td>
<td>0.41**</td>
</tr>
<tr>
<td>PRL</td>
<td>0.18</td>
</tr>
<tr>
<td>LH</td>
<td>−0.05</td>
</tr>
<tr>
<td>FSH</td>
<td>−0.14</td>
</tr>
<tr>
<td>TSH</td>
<td>0.11</td>
</tr>
<tr>
<td>ACTH</td>
<td>0.19</td>
</tr>
<tr>
<td>α-SU</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**P < 0.01.

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**Figure 1** PTTG expression in pituitary adenomas. RT-PCR products generated using primers described in Table 1 were electrophoresed on a 1.6% agarose gel containing 0.5 μg/ml ethidium bromide, then photographed under ultraviolet light; PCR products were excised and verified by automated sequencing. The gel represents the typical appearance of PTTG expression in pituitary tumour subtypes. Lanes 1 and 2, non-functioning adenomas (nos 34 and 39 respectively); lanes 3 and 4, somatotroph adenomas (nos 7 and 6); lanes 5 and 6, lactotroph adenomas (nos 21 and 19); lane 7, a corticotroph adenoma (no. 15); M, 100 bp DNA ladder; GAPDH, human GAPDH positive control.

**Figure 2** PTTG expression in pituitary tumour subtypes. PTTG expression relative to the control GAPDH is shown as individual values for each tumour. Mean expression within each tumour subtype group is shown by the horizontal line. The differences between the means were analysed by ANOVA.

**Figure 3** VEGF secretion in relation to PTTG expression. *In vitro* secretion of VEGF (pg/10^6^ cells per 24 h) was compared with the expression of PTTG (relative to GAPDH) in 16 pituitary tumours (nine non-functioning, two corticotroph, four somatotroph and one lactotroph adenoma). The calculated Spearman rank correlation coefficient was r = 0.156, *P* = NS.
activation of the GH gene. Although PTTG was expressed in all tumour types, there was no correlation with any other hormone secreted in vitro. The numbers of corticotroph and lactotroph tumours studied were relatively small in this series (n = 5 for each tumour type) and further studies may be required to confirm conclusively this lack of correlation of PTTG expression with in vitro secretion of hormones other than GH.

Earlier studies have suggested a relationship between PTTG expression and tumour invasiveness (15) or tumour recurrence (21), suggesting a potential role for PTTG expression as a prognostic marker in surgically excised pituitary tumours. We used a well-validated quantitative method (16) for determining tumour volume from pre-operative MRI scans in 19 of the tumours from our series. We were unable to demonstrate a correlation between tumour volume and relative level of PTTG expression, although tumour volume does not necessarily indicate tumour recurrence or invasiveness and more detailed radiological studies are required to examine the role of PTTG as a useful predictor of tumour prognosis or recurrence.

VEGF induces angiogenesis and increases vascular permeability and endothelial cell proliferation. It is considered to be the most important angiogenic factor involved in the neovascularisation of solid non-pituitary tumours. Little is known about the role of angiogenesis or VEGF in pituitary tumour development and progression. One report states that in marked contrast to other tumours, pituitary adenomas are less vascular than the normal pituitary gland (24). In situ hybridisation and immunocytochemical studies of the normal human pituitary have demonstrated the expression of VEGF in all cell types, but mainly in somatotrophs, corticotrophs and folliculostellate cells (19). Other investigations have revealed that decreased VEGF expression occurs in adenomas compared with non-tumourous pituitary but that pituitary carcinomas show increased levels of VEGF expression relative to adenomas suggesting up-regulation of VEGF during pituitary tumour progression (12). In contrast, a recent study has shown markedly raised VEGF mRNA in non-functioning tumours compared with normal pituitaries (14). These findings are at variance with protein studies (12) and our own data, which failed to show any association between VEGF protein production from the cultured tumour cells and tumour type. Since PTTG is reported to induce angiogenesis (7), we were interested in determining any potential inter-relationship between PTTG and VEGF. We found measurable basal production of VEGF in all tumours studied but no correlation with PTTG expression or
tumour size. One other recent study has also reported VEGF production from all types of pituitary adenomas (11) but as with our study there was no significant difference between the different tumour types, nor were there any significant differences demonstrated in VEGF secretion between micro- and macroadenomas or between invasive and non-invasive tumours. Thus it seems unlikely that VEGF-mediated angiogenesis plays a major role in pituitary tumour progression and this may explain the usually slow growth rate of these adenomas. Alternatively, development and progression of these adenomas may not be dependent on vascularisation. In normal pituitary, VEGF is found in folliculostellate cells (19, 20) and our finding of a significant correlation between VEGF and S100 protein secretion would suggest that folliculostellate cells in the tumour culture might have been the source of VEGF production. Folliculostellate cells are seldom found in pituitary adenomas but accumulate in a transition zone at the boundary of the tumours (25). It is possible that VEGF production by folliculostellate cells within this transition region may be regulated during tumourigenesis and further studies are needed to explore this.

In conclusion, we have confirmed the presence of PTTG in pituitary adenomas and demonstrated a higher level of expression in somatotroph tumours and a significant correlation with GH production. We failed to demonstrate a relationship between PTTG expression and tumour volume or with production of the angiogenic factor VEGF. Thus although PTTG induces an angiogenic phenotype in both in vitro and in vivo angiogenesis models, it seems unlikely that a VEGF-mediated angiogenic mechanism occurs during pituitary tumour progression.

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