Preclinical and clinical experiences with the role of dopamine receptors in the treatment of pituitary adenomas

Diego Ferone, Rosario Pivonello¹, Eugenia Resmini, Mara Boschetti, Alberto Rebora, Manuela Albertelli, Valeria Albanese, Annamaria Colao¹, Michael D Culler² and Francesco Minuto

Department of Endocrinological and Medical Sciences and Center of Excellence for Biomedical Research, University of Genova, Genova, Italy, ¹Department of Molecular and Clinical Endocrinology and Oncology 'Federico II' University, Naples, Italy and ²Biomeasure Inc./IPSEN, Milford, Massachusetts, USA

(Correspondence should be addressed to Diego Ferone; Email: ferone@unige.it)

Abstract

Pituitary tumors can cause symptoms of mass effect and hormonal hypersecretion that can be reversed with surgical resection or debulking of the adenoma, radiotherapy, or medical treatment. Medical treatment is the primary choice for prolactinomas because dopamine agonists are very effective in the treatment of these tumors, with rates of control (tumor size reduction and hormone suppression) as high as 80–90% for microprolactinomas and 60–75% for macroprolactinomas. The function of dopamine receptors in other histotypes of pituitary adenoma is still debated. However, new insights into receptor physiology and the introduction of new clinically available, as well as experimental, compounds have reopened a potential role of dopaminergic drugs in the medical treatment of pituitary tumors. The differences between the effectiveness and the resistance to different dopaminergic agents, the new challenging results from clinical and experimental studies, as well as the future of dopamine agonists in the therapy of pituitary tumors are discussed.

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Introduction

The therapeutic strategy for pituitary adenomas includes surgery, radiotherapy, and medical therapy. Therefore, a combination of treatments may be required to attain the therapeutic goal. Among the medications, dopamine agonists represent the first generation of effective drugs used in the treatment of pituitary tumors. The introduction of this class of compounds was based on the evidence that in the hypothalamic–pituitary system, the neurotransmitter/neuromodulator dopamine inhibits pituitary hormone secretion, in particular prolactin (PRL)- and proopiomelanocortin-derived hormones. It is well known that dopamine agonists, such as bromocriptine, pergolide, terguride, lisuride, quinagolide and cabergoline, can inhibit PRL secretion by binding to the D₂ dopamine receptors (D₂) located on both normal and pituitary adenoma cells (1). Moreover, they can effectively decrease excessive PRL secretion, as well as the size of the tumor in patients with prolactinoma (2). Furthermore, dopamine agonists can also be used in the treatment of patients with other

pituitary tumor histotypes although less frequently. The major requirement for its use is that the tumor cells should express D₂ receptors. Therefore, in addition to prolactinomas, targets of dopamine agonist therapy are somatotrope tumors, nonfunctioning pituitary tumors, corticotrope pituitary tumors including Nelson's syndrome, gonadotropinomas and thyrotropin-secreting pituitary tumors (2). Different dopaminergic agents have been introduced into clinical practice over the last decades, and the role of this group of compounds has been recently renewed due to the availability of novel clinical as well as experimental molecules, representing one of the most interesting future perspectives for the medical therapy of pituitary tumors.

Dopamine receptors

Dopamine receptors (DRs) belong to the family of G protein coupled receptors and they modulate the activity of adenylate cyclases through G proteins. Based on their interaction with adenylate cyclase, the five known DRs are divided into two subfamilies: the D₁-like (D₁ and D₅) and the D₂-like (D₂, D₃ and D₄) receptors. D₁-like receptors stimulate adenylate cyclase activity through G_s proteins, while D₂-like receptors decrease intracellular cAMP accumulation through G_i/G_o proteins (1). The D₂ receptor exists in two

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different isoforms: long ($D_{2\text{long}}$) and short ($D_{2\text{short}}$). D_2 isoforms differ in the presence or absence of a stretch of 29 amino acids in the third cytoplasmic loop, involved in G protein receptor coupling (1). The two D_2 isoforms may be associated with different intracellular signaling transduction mechanisms and therefore elicit different effects after binding to dopamine agonists (1). The five DR subtypes have a different tissue distribution pattern and play multiple roles in various organs and tissues. The D_2 receptor is expressed in the anterior and intermediate lobes of the pituitary gland, where it mediates the tonic inhibitory control of hypothalamic dopamine on PRL and MSH secretion respectively (1). In particular, $D_{2\text{short}}$ and $D_{2\text{long}}$ receptor isoforms are expressed in both melanotrope and lactotrope cells, where the longer form is predominant. Moreover, subpopulations of lactotropes have been identified which express different $D_{2\text{long}}/D_{2\text{short}}$ mRNA ratios. The D_4 receptor is also expressed in the anterior pituitary; however, its role is still unknown (1).

Multiple signal transduction mechanisms are activated by D_2 receptors in the pituitary gland. In addition to the inhibition of adenylate cyclase, D_2 receptors, via G protein-dependent mechanisms, inhibit phosphatidylinositol metabolism, activate voltage-activated potassium and decrease voltage-activated L- and T-type calcium currents.

The presence of D_2 receptors which mediate inhibition of PRL secretion by the anterior pituitary gland has led to the first and major therapeutic application of dopamine agonists in the treatment of hyperprolactinemia due to functional hypothalamus–pituitary alterations or the presence of PRL-secreting tumors. Indeed, D_2 receptor agonists are the most effective pharmacological tools to normalize serum PRL levels in these patients (reviewed in Ref. 3). Furthermore, the major biochemical defects contributing to dopamine agonist resistance in prolactinomas seem to be either the decreased density or the absence of D_2 receptors (1). In fact, mutations in the D_2 receptor gene have not been observed in PRL- or GH/PRL-secreting pituitary tumors (4).

Bromocriptine, one of the first generation dopamine agonists, has been widely used for the treatment of pituitary tumors. It binds both D_1 and D_2 receptors, whereas cabergoline and quinagolide are more selective for the D_2 receptor. However the latter compounds have a longer duration of action and are better tolerated than bromocriptine (2).

Pituitary scintigraphy using *in vivo* D_2 targeting agents may indicate the expression of DRs in pituitary tumors and select patients potentially responsive to treatment with dopamine agonists (5–7). However, it is an expensive technique and its value has been recently weakened, particularly for clinically nonfunctioning adenomas (NFAs; 8, 9). In spite of the limited significance in clinical practice, these data support the concept that the receptor pattern has a key role for the choice of the most appropriate treatment schedule and for a successful medical therapy (10). Whereas *in vitro*,

besides ligand-binding and molecular biology techniques, availability of subtype-specific antibody to D_2 seems to offer a new easier method to evaluate the receptor profile, at least in those pituitary adenomas that are unsuccessfully operated (11).

Role of DRs in pituitary adenomas

Prolactinomas Hyperprolactinemia is commonly found in both female and male patients with abnormal sexual and/or reproductive function, or with galactorrhea. If serum PRL levels are above 200 $\mu\text{g/L}$, prolactinoma is the underlying cause; if the levels are lower, different diagnoses include drug interference, compression of the pituitary stalk by other pathology, hypothyroidism, renal failure, cirrhosis, chest wall lesions, or idiopathic hyperprolactinemia (3, 12). Prolactinomas account for ~40% of all pituitary adenomas and are an important cause of hypogonadism and infertility. When a pituitary tumor is present, patients often have pressure symptoms in addition to endocrine dysfunction, such as headaches, visual field defects or cranial nerve deficits. The majority of patients with prolactinomas, both micro- and macro-, can be successfully treated with dopaminergic drugs as first-line treatment, resulting in normalization of PRL secretion and gonadal function and with significant tumor shrinkage in a high percentage of cases (3). Dopamine agonist therapy for PRL excess has been developed over the last three decades. The inhibition of cAMP levels is a key step in the inhibition of PRL release by dopamine; therefore, it is likely that all dopaminergic ergot derivatives share similar mechanisms of action. The earlier therapies such as bromocriptine have been virtually replaced now by the newer dopamine agonist cabergoline, which has the most favorable profile, followed by quinagolide. Moreover, it has been shown that shrinkage of macroprolactinoma during cabergoline treatment is greater in naive patients than in patients pre-treated with other dopamine agonists (13). Dopamine agonists reduce the size of prolactinomas by inducing a reduction in cell volume (through inhibition of gene transcription and PRL synthesis), as well as by causing perivascular fibrosis and partial cell necrosis. There may also be a true antimitotic effect of these drugs. Histologically, there is a reduction in secretory activity and cell size, an increase in immunoreactive PRL cellular content, and inhibition of exocytosis. Moreover, dopamine agonists also seem to possess proapoptotic capabilities in prolactinomas, even after short-term treatment (14). If PRL levels are well controlled with dopamine agonist therapy, gradual tapering of the dose to the lowest effective amount is recommended. In a

number of cases, medication can be stopped after several years, particularly in patients treated with cabergoline showing normalization of PRL levels and no evidence of tumor during magnetic resonance imaging examination (15). In the small group of patients who do not respond to this treatment or who refuse long-term therapy, surgery is offered, as radiotherapy has only a limited value (3).

In general, prolactinomas exhibit varying degrees of responsiveness to the dopamine agonists, ranging from complete response at one end to total resistance at the other. The majority of patients found to be resistant to bromocriptine subsequently respond to cabergoline. Moreover, treatment with cabergoline offers a greater chance of obtaining permanent remission and successful withdrawal of medication, compared with treatment with bromocriptine (15).

The concept of dopamine agonist resistance must be distinguished from that of dopamine agonist intolerance, in which adverse effects play the most relevant role. The responsibility of true dopamine agonist resistance is with the lactotrope dopamine D₂ receptor itself, mainly the reduced density of D₂ receptors, whereas it is still unclear whether receptor alterations, leading to changes in affinity and/or in the downstream signaling effectors, are involved (3).

GH-secreting adenomas In the late 1970s, the introduction of DR agonists made it possible to reduce GH secretion from somatotropinomas for the first time. Therefore, dopamine agonists represent the first effective medical treatment for acromegaly (12, 16), until the availability of somatostatin analogs. Moreover, the role of dopaminergic agents in acromegaly has been recently renewed with the introduction of cabergoline and with the novel insights into DR pathophysiology.

The effectiveness of dopamine agonists is related to the expression of D₂ receptor on a subset of somatotrope adenomas, and the presence of such receptors correlates with response to therapy. Advantages of these agents include the availability of an oral formulation and a lower cost compared with other medical options. Generally, bromocriptine normalizes IGF-I levels in about 10% of cases (12, 16). In a comparative study, long-term treatment with quinagolide or cabergoline or long-acting bromocriptine depot preparation caused a significant decrease in GH and IGF-I; however only quinagolide normalized circulating hormones, in 43.8% of treated patients (17). From this study, quinagolide apparently resulted as the most effective drug. However, the low dose of cabergoline and bromocriptine used limited the value of this comparative study between the three dopaminergic drugs. The dosage of bromocriptine required to achieve IGF-I normalization is often high (20–40 mg/day) and usually poorly tolerated because of gastrointestinal discomforts or headache. As a result, the role of bromocriptine seems to be limited in the treatment of

acromegaly. Conversely, in another study on a larger population, higher doses of cabergoline normalized IGF-I in 39% of patients with acromegaly, but improved responses were detected primarily in those patients with slight IGF-I elevations and concomitant hypersecretion of PRL (18). Cabergoline seems to be more effective than other dopamine agonists in acromegaly not only in normalizing hormone levels, but also in inducing significant tumor shrinkage (19). The co-secretion of PRL (in ~40% of adenomas from acromegalic patients) has often been suggested to predict improved response to dopamine agonists. However, more recent evidences are driving down the potential role of both circulating PRL levels and PRL positivity at immunohistochemistry in discriminating patients with a better response to dopaminergic drugs (20). Once again, the GH-IGF-I-lowering effect of dopamine agonist treatment can be accounted for by the expression and binding of the drug to D₂ receptors, present not only in mixed GH/PRL tumor or somatomammotrope adenomas, but also in 30% of adenomatous 'pure' GH-secreting cells (20). Indeed, we have recently demonstrated in a large series of tumors from acromegalic patients a positive correlation between D₂ expression and the sensitivity of GH and PRL secretion to quinagolide, as well as between somatostatin receptor 2A expression and the sensitivity of GH and IGF-I secretion to somatostatin analog treatment. Conversely, the presence of PRL was not correlated with the tumor sensitivity to dopamine agonists, suggesting that the response to therapy might be affected by other elements (21, 22). This finding is in line with the evidence reported by Trouillas *et al.* using five lineages of SMtTW tumors that are representative of the most frequent tumors encountered in human pituitary pathology (23). These authors found a full concordance between tumor responses to bromocriptine and the expression of D₂ receptor by the tumors. They also identified a tumor lineage with a malignant phenotype, secreting high amounts of PRL and presenting a resistance to bromocriptine, supporting the idea that dopamine agonist-resistant prolactinomas are aggressive tumors (23).

The usefulness of the association of dopamine agonists plus somatostatin analogs has been clearly demonstrated by several studies and is extensively reviewed by Colao *et al.* in another article of the present issue.

Clinically nonfunctioning adenomas NFAs are the most prevalent form of pituitary macroadenomas. They are devoid of a specific clinical syndrome related to hormonal hypersecretion and, hence, most patients are diagnosed late in the course of their disease, when the tumor is already large enough to cause mass-related signs and symptoms. Surgery is the first line of treatment, but unfortunately it is not curative in the majority of patients, even in the best neurosurgical centers. Radiotherapy is the only modality shown to be effective in the prevention of residual tumor growth. However, it is

contraindicated in several cases and hypopituitarism is often recorded after radiation therapy.

The characterization and classification of this large and assorted group of tumors has significantly changed in the last few years, thanks to the availability of more sensitive techniques showing that the majority of these tumors indeed secrete FSH and/or LH or their respective α - and β -subunits. However, secretion by these tumors is minimal or inefficient and the clinical behavior is that of an inactive tumor. Gonadotrope adenomas account for 10–15% of all pituitary adenomas, whereas 5–10% of all tumors are truly nonfunctional and are referred to as null cell adenomas (24). When studied *in vivo*, gonadotrope adenomas are identified on the basis of hypersecretion of FSH or LH, α - or β -subunit in the basal state or after dynamic stimulation with TRH. *In vitro* studies performed on surgically resected tumor tissue (immunohistochemistry or molecular biological techniques) have allowed a broader characterization of these adenomas showing positive staining but no measurable hormone secretion in some tumors (25). Therefore, silent corticotrope and somatotrope adenomas have been easily recognized as well (25). Ligand-binding studies and scintigraphic evaluations have previously shown the presence of somatostatin as well as dopamine-binding sites (mainly D_2 receptor) in NEAs (5–7). More recently, sophisticated techniques have confirmed the heterogeneous expression of DRs in NEAs, and the effects of dopamine agonists in these tumors were investigated both *in vivo* and *in vitro* (26, 27). Conflicting results have been reported with respect to the effect of dopamine agonists on the growth of NEAs. In some clinical studies, no effect on the tumor size could be found, whereas in others tumor shrinkage was reported in up to 20% of the patients (28). In particular, long-term treatment of patients with NEA with high doses of quinagolide could not prevent progressive increase in tumor size in most patients, despite persistent suppression of hormone secretion (29). In addition, Renner *et al.* have suggested for the first time that the presence of the $D_{2\text{short}}$ isoform in the NEAs improves the growth-suppressive response to bromocriptine *in vitro* (26). This finding has been subsequently confirmed in a large series of cases evaluated *in vitro* for the receptor content, demonstrating D_2 receptor expression in nearly 70% of cases, and tested *in vivo* for the sensitivity to cabergoline (27). The expression of $D_{2\text{short}}$ rather than $D_{2\text{long}}$ isoform was found to be associated with the most favorable response of the tumor to cabergoline treatment (27). More recently, dopamine agonist therapy has been found to be associated with a decreased prevalence of residual tumor enlargement in patients with NEAs, particularly when treatment was initiated before the detection of tumor remnant growth (30). These authors suggested the routine use of dopaminergic drugs to prevent residual mass expansion in patients unsuccessfully operated for NEAs (30).

Recently, a hybrid somatostatin/dopamine molecule, BIM-23A387, has been tested *in vitro* in cultures of NEAs, where it affected the viability of some, but not all, pituitary adenoma cells (31). The chimeric compound exerted roughly similar inhibitory effects compared with bromocriptine (31). We have also tested two somatostatin/dopamine hybrid compounds in different series of pituitary adenomas (Fig. 1). Preliminary data seem to confirm the higher potency of these new chimeric molecules compared with the clinically available dopamine agonists and somatostatin analogs, particularly in inhibiting hormone secretion in cell cultures of selected NEAs and GH-secreting pituitary adenomas (Ferone *et al.* unpublished observations).

Adrenocorticotropin (ACTH)- and thyrotropin (TSH)-secreting adenomas Treatment with bromocriptine has been also investigated in ACTH-secreting or corticotrope pituitary tumors, although with controversial results (32–34). However, the first study evaluating DR expression and the effect of cabergoline treatment in controlling the ACTH and cortisol

Figure 1 *In vitro* effects on α -subunit (α -SU) secretion of cabergoline (CAB), octreotide, (OCT), octreotide plus cabergoline (OCT + CAB), BIM-23A387 and BIM-23A760 in primary cultures derived from three patients with clinically nonfunctioning pituitary adenomas. Cell suspensions of the pituitary adenoma tissues were prepared by enzymatic dissociation with collagenase. For short-term incubation of monolayer cultures, the dissociated cells were plated onto collagen-coated 48-well plates (Costar, Cambridge, MA, USA) at a density of 10^4 cells/well per 1 ml culture medium to study hormone secretion. After 2 days, test substances were added in fresh medium at concentrations of 10^{-8} M, and at the end of 6-h incubation, the medium was removed and centrifuged for 5 min at 600 g. The supernatant was collected and stored at -20°C until the determination of α -subunit concentration.

α -Subunit immunoreactivity was measured in the medium from cultured pituitary cells incubated with or without the above-mentioned drugs (conditioned media). Hormone assays were performed in duplicate after appropriate sample dilutions of conditioned medium from treated cells. Results were obtained by determining the mean value among four replicates. Data are expressed as mean $\pm$ S.E.M. BIM compounds were provided by Biomeasure, Inc. (Milford, MA, USA). BIM-23A387 and BIM-23A760 are chimeric molecules that combine structural elements of both somatostatin and dopamine and retain affinity for both sst_2 and D_2 , and sst_2 , sst_5 , and D_2 respectively (41).

hypersecretion associated with corticotrope pituitary tumors has shown that the cabergoline-responsive cases were associated with D₂ expression, whereas almost all cases not responsive to cabergoline showed absent D₂ expression (11). In this study, functional D₂ receptors were expressed in ~80% of corticotrope pituitary tumors, and the effectiveness of cabergoline in normalizing cortisol secretion in 40% of cases supports its therapeutic use in the management of persistent and/or recurrent Cushing's disease (11). The successful rates observed with bromocriptine in an early study (32) and with cabergoline in a recent one (11) is, therefore, based on the presence of functional D₂ receptors on corticotropes. However, the different molecular, biochemical and pharmacological properties of cabergoline, particularly the higher specificity and affinity for D₂ receptor and the longer duration of action, make the latter dopaminergic drug preferable to bromocriptine (35).

A dramatic tumor shrinkage has been also reported in a case of silent corticotrope tumor during cabergoline therapy (36). The *in vitro* studies on tumor tissue from the adenoma provided evidence of D₂ receptor expression within the tumor with an intensity comparable to that found in control prolactinomas (36). Similarly, treatment with cabergoline for one year induced normalization of plasma ACTH levels and disappearance of the pituitary tumor in a patient with Nelson's syndrome (37). The direct effect exerted by cabergoline treatment on the remission of Nelson's syndrome was proven by treatment withdrawal, showing a significant increase in ACTH levels after 3 months, suggesting that cabergoline may be a valid therapeutic alternative in this syndrome as well (37).

The presence of DRs in TSH-secreting adenomas has represented the rationale for therapeutic trials with dopamine agonists such as bromocriptine and cabergoline. Several studies have shown a large heterogeneity of TSH responses to dopaminergic agents either in primary cultures or *in vivo* (38). From a clinical viewpoint, dopamine agonists and cabergoline in particular have been employed in some TSH-secreting adenomas with variable results, positive effects being mainly observed in some patients with mixed PRL/TSH adenoma, whereas tumor shrinkage was documented in few cases (38).

The effects of dopamine agonists should be re-evaluated in light of the demonstration of heterodimerization of somatostatin receptor subtype 5 and dopamine D₂ receptor (39). This phenomenon also seems to be linked with an enhanced functional activity of these receptor dimers (39). Indeed, the above-mentioned new hybrid compounds, that contain structural elements of both somatostatin and dopamine and retains potent selective agonist activity at both the somatostatin and DRs, displayed a higher potency compared with classical analogs in inhibiting hormone secretion and controlling

cell proliferation in different cell models *in vitro*, including pituitary adenomas (40, 41). Receptor characterization will be necessary to understand the mechanisms regulating the response to medical therapy, particularly considering the future availability of these compounds (new somatostatin analogs and chimeric molecules) with specific receptor-binding profiles.

Conclusions

During recent years, the role of DRs in pituitary adenomas has been restored not only in light of the new insights into receptor pathophysiology, but also due to the availability of novel sophisticated technologies that are able to reveal novel potential mechanisms of action. The inhibitory effects of dopamine agonists on pituitary cells are mainly mediated through D₂ receptors. On the other hand, other receptor subtypes have been detected at the pituitary level and the interaction of DRs with other neuropeptide receptors may reopen the discussion on the medical therapy of pituitary adenomas (27, 39–41). Dopamine agonists inhibit hormone release and induce tumor shrinkage in most PRL-secreting adenomas, whereas in other adenoma types such effects are less represented. Studies on D₂ gene expression in different types of pituitary adenomas showed a variable D₂ expression localized in the cytoplasm and nuclei of a large number of adenomas; however, the significance of nuclear localization of D₂ protein remains unclear (42). Moreover, recent preliminary data suggest that both isoforms of dopamine D₂ receptors are involved in the signaling pathways involved in the antiproliferation and cell death in pituitary tumor cells, possibly through p38 MAPK and ERK activation (43). The complete characterization and definition of the molecular basis of these signaling pathways may allow the mechanisms of the dopaminergic control of cell proliferation and cell death to be understood, particularly in pituitary tumors. Moreover, it is of interest to know whether the inclusion of the dopaminergic moiety in new somatostatin analogs could result in prolonged pharmacological properties of these chimeric molecules, or even activate alternative intracellular signaling pathways involved in the control of cell growth (40). Further studies on receptor expression and functionality in a larger population of patients with pituitary tumors are needed to better define patients who could benefit from dopamine agonists as a therapeutic option for pituitary adenomas.

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