REVIEW

The clinical–molecular interface of somatostatin, dopamine and their receptors in pituitary pathophysiology

Diego Ferone, Federico Gatto, Marica Arvigo, Eugenia Resmini, Mara Boschetti, Claudia Teti, Daniela Esposito and Francesco Minuto

Department of Endocrinological & Medical Sciences (DiSEM) and Center of Excellence for Biomedical Research, University of Genova, Viale Benedetto XV, 6, 16132 Genova, Italy

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

Abstract

The role of somatostatin and dopamine receptors as molecular targets for the treatment of patients with pituitary adenomas is well established. Indeed, dopamine and somatostatin receptor agonists are considered milestones for the medical therapy of these tumours. However, in recent years, the knowledge of the expression of subtypes of somatostatin and dopamine receptors in pituitary adenomas, as well as of the coexpression of both types of receptors in tumour cells, has increased considerably. Moreover, recent insights suggest a functional interface of dopamine and somatostatin receptors, when coexpressed in the same cells. This interaction has been suggested to occur via dimerisation of these G-protein-coupled receptors. In addition, there was renewed interest around the concept of cell specificity in response to ligand-induced receptor activation. New experimental drugs, including novel somatostatin analogues, binding to multiple somatostatin receptor subtypes, as well as hybrid somatostatin–dopamine compounds have been generated, and recently a completely novel class of molecules has been developed. These advances have opened new perspectives for the medical treatment of patients with pituitary tumours poorly responsive to the present clinically available drugs, and perhaps also for the treatment of other categories of neuroendocrine tumours. The aim of the present review is to summarise the novel insights in somatostatin and dopamine receptor pathophysiology, and to bring these new insights into perspective for the future strategies in the medical treatment of patients with pituitary adenomas.

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Introduction

Somatostatin (SRIF) and dopamine (DA) are two critical regulators of pituitary cells function, being involved in the negative control of hormonal secretion of the anterior pituitary (Ben-Jonathan & Hnasko 2001, Guillemin 2005). The actions of SRIF and DA are mediated by specific G-protein-coupled receptors (GPCR) that are present on the cells of both the normal gland and of the pituitary adenomas: SRIF receptor (SSR) subtypes 1, 2, 3 and 5 (sst1–5; Miller et al. 1995, Hofland & Lamberts 2001); and the subtype 2 (D2) of DA receptors (DR; Missale et al. 1998). Conversely, the expression of sst2 is rather infrequent, whereas D2 receptor has also been found expressed in the anterior pituitary and in a small subset of pituitary tumours (Missale et al. 1998, Pivonello et al. 2004b); however, its role in the pathophysiology of the pituitary has not been examined yet. Two different isoforms of sst2 and D2 have also been found and characterised: the two forms of the sst2 (sst2A and sst2B) and of D2, the long (D2long) and short (D2short) isoforms, are generated via alternative splicing (Missale et al. 1998, Hofland & Lamberts 2003). While sst2B is almost unexpressed in humans, the two D2 isoforms may be coexpressed and associated with different intracellular signalling transduction mechanisms, and may, therefore, elicit different effects after binding with DA agonists (Missale et al. 1998).

As for the physiological lineaments, SRIF, interacting with SSRs, inhibits the secretion of a wide range of hormones, including the pituitary GH, PRL and TSH. Signalling through SSRs is multifaceted. Indeed, binding of SRIF or SRIF analogues to SSRs initiates a complex set of signalling events triggered by the interaction of the activated receptors with a large number of different protein partners, involving firstly specific G-protein activation (Moller et al. 2003). As a consequence, the activities of several key enzymes, including adenyl cyclase, phosphotyrosine phosphatases (PTPases) and mitogen-activated protein kinase (MAPK) are modulated along with changes in the...
intracellular levels of calcium and potassium ions (Florio 2008). G proteins, via the stimulation of PTPases, may also produce some of the cytostatic actions of SRIF (Fig. 1A). For example, in pituitary tumour cells, SRIF analogues produce their anti-proliferative action by acting on the phosphatidylinositol 3-kinase (PI3K)/AKT signalling pathway (Theodoropoulou et al. 2006). Whereas, more recently, apoptosis has been also observed upon binding of SRIF and SRIF analogues to sst3, and possibly to sst2 as well. (Fig. 1A). Which type of signalling prevails in given cells depends on the cell-specific distribution of SSR subtypes and signalling elements, as well as on SSRs internalisation, desensitisation and/or receptor crosstalk (Lahlou et al. 2004, Schonbrunn 2008). Finally, the subcellular expression pattern of SSR subtypes and their activity in response to agonist treatment may also be affected by intracellular complements, such as proteins involved in intracellular vesicle trafficking (e.g. β-arrestin). Indeed, different SRIF analogues may induce distinct conformations of the receptor/ligand complex, preferentially coupled to either receptor signalling or receptor endocytosis (Tulipano & Schulz 2007).

The D2 receptor is important for mediating the effects of DA to control movement, certain aspects of behaviour in the brain and PRL secretion from the anterior pituitary. Multiple transduction mechanisms are activated by D2 receptors in the pituitary. In addition to inhibition of adenylyl cyclase, pituitary D2 receptors inhibit PI metabolism, stimulate voltage-activated potassium channels and decrease voltage-activated L-type and T-type calcium currents (Fig. 1B). All these effects are mediated by G proteins (Missale et al. 1998). Studies on D2 gene expression in different types of pituitary adenomas showed a variable D2 expression localised in the cytoplasm and nuclei of a large number of adenomas. However, the significance of nuclear localisation of D2 remains unclear (Ferone et al. 2007a). Moreover, both isoforms of D2 receptor are relevant to the signalling pathways involved in the proliferation and

![Figure 1](image-url)
cell death of pituitary tumour cells, possibly through p38 MAPK and ERK activation (Ferone et al. 2007a).

Along the last decades, the knowledge on the pathophysiology of these two families of GPCRs in the pituitary has progressively increased due to the synthesis and availability of specific subtypes receptor agonists and antagonists, useful not only in experimental settings, but also of incredible value in clinical practice as potent therapeutic agents. However, until recently, each receptor molecule was believed to interact separately with G proteins, while a series of observations have challenged this conclusion. Indeed, the emerging concept that these GPCRs may also function as homo- and heterodimers has opened a complete new scenario for those trying to interpret confusing results obtained in vivo or in isolated tissues that do not seem to obey the classical binding and activation patterns described for individual cloned receptors.

The clinical–molecular interface of SRIF, DA and their receptors in pituitary pathophysiology will be discussed in this review, because it represents an ideal model of the possibility of a whole new level of complex interactions that could multiply the range of activities of the already large family of GPCRs.

Heterogeneity of somatostatin and D2 dopamine receptor distribution in pituitary adenomas

Both SSRs and D2 receptors are significantly expressed in pituitary adenomas, even if there is a large interstudy variability reflecting not only the different sensitivity of the techniques employed, but also the compelling heterogeneity of these tumours (Stefaneanu et al. 2001, Moller et al. 2003, Saveanu et al. 2008).

In most GH adenomas, sst2, sst3, and D2 coexpression has been found, at both mRNA and protein levels, however, half of GH tumours also coexpress sst3 and sst1, particularly mixed GH/PRL adenomas (Panetta & Patel 1995, Stefaneanu et al. 2001, Zatelli et al. 2005, Taboada et al. 2007, Ferone et al. 2008, Saveanu et al. 2008). The vast majority of prolactinomas express high number of D2 receptor; however, sst1, and particularly sst5, are also notably present, while sst2 is only expressed in a minority of them (Miller et al. 1995, Panetta & Patel 1995, Stefaneanu et al. 2001, Fusco et al. 2007, Saveanu & Jaquet 2008). Non-functioning pituitary adenomas (NFPAs), including gonadotrophinomas, as well as α-subunit producing tumours, express mainly sst3 and, at a lesser degree, sst2, seldom associated with sst1 (Zatelli et al. 2004, Taboada et al. 2007). The D2 receptor is expressed in most clinically NFPAs, and, interestingly, heterogeneous D2 isoform expression has been demonstrated in these tumours, in which D2_short seems more favourable than D2_long expression for both in vitro and in vivo growth inhibitory response to DA agonists (Renner et al. 1998, Pivonello et al. 2004a, Taboada et al. 2007). In Cushing’s disease, corticotroph adenomas mainly express sst3 and D2 receptors, whereas sst5 is expressed at lower levels together with sst1 and sst3 (Stefaneanu et al. 2001, Pivonello et al. 2004a, Batista et al. 2006, de Bruin et al. 2009). Both sst5 and D2 receptors seem to play an important role in the regulation of ACTH release, at least in a subset of specific pituitary area-derived corticotroph tumours (Pivonello et al. 2004a, de Bruin et al. 2009). Interestingly, SSRs and D2 receptor seem differentially regulated by glucocorticoids in neuroendocrine cells (de Bruin et al. 2008a). This aspect should be taken into account because cortisol-lowering therapy could indirectly affect the responsiveness of tumour’s cells to drugs targeting these receptors. Moreover, recently, it has been proposed that canine corticotroph adenomas may provide a model to study corticotroph cell pathophysiology (de Bruin et al. 2008b). However, since distinct differences do exist between human and canine corticotroph adenomas in terms of SSR and D2 receptor expression and regulation, as well as the relative responses to SRIF and DA agonists, these differences should be carefully considered when using dogs as a model to evaluate efficacy of novel SRIF and DA agonists in human Cushing’s disease (de Bruin et al. 2008b). D2 receptors have been found at very low density and with a different distribution of the two isoforms in the rare TSH-secreting tumours as well, where, on the contrary, sst1, and especially sst2 and sst3, are significantly represented (Panetta & Patel 1995, Stefaneanu et al. 2001, Yoshihara et al. 2007, Saveanu et al. 2008).

Although the above-mentioned high variability may be due in part to the different techniques used in these studies (mainly mRNA analysis by northern blot, in situ hybridisation and real-time PCR, or protein assays, such as radioactive-binding studies, and, more recently, immunohistochemistry), an apparently rather complex situation came out because of the great heterogeneity of these tumours.

However, when we examine more deeply these data, a reliable pattern apparently emerges. The D2 receptor is the GRCP mostly represented in the pituitary tumours, and is overall associated with two or more SSR subtypes in the different adenoma categories, possible following preferential outline in certain subclasses: sst2 and sst3 are linked with D2 in the majority of somatotroph tumours, D2 is coexpressed with sst1 and sst3 in prolactinomas, and with sst3 and sst2 in NFPAs, finally D2 and sst3 are almost equally represented in corticotroph tumours (Zatelli et al. 2005, de Bruin et al. 2009, Ferone et al. 2008, Saveanu et al. 2008; Fig. 2).
Functional role of somatostatin and D2 dopamine receptors in pituitary adenomas and implications for therapeutic strategies

It is, however, intriguing that the observations arising from studies of characterisation of the receptor profile in pituitary tumours did not always correlate with the efficacy expected for the corresponding medical therapy.

In fact, while dopaminergic drugs are efficient in more than 90% of prolactinomas (Gillam et al. 2006), SRIF analogues, octreotide and lanreotide control about 80% of TSH-secreting adenomas (Beck-Peccoz & Persani 2002, Ness-Abramof et al. 2007), but only 60% of GH-producing tumours (Freda 2002, Burt & Ho 2006). Moreover, clinically available SRIF analogues or DA agonists have a minor role in the medical treatment of NFPAs, since they have been shown to control the growth of less than 20% of this tumour type (Colao et al. 2008). However, it has been also shown that DA agonist therapy is associated with a decreased prevalence of residual tumour enlargement in patients with NFPAs, particularly when treatment is instituted before tumour remnant growth is detected (Greenman 2007). On the other hand, although still in lower percentage compared with other pituitary adenomas, at least cabergoline, a D2-selective second-generation DA agonist, seems able to control a specific subset of corticotroph pituitary tumours (Pivonello et al. 2004a, de Bruin et al. 2009). Similarly, a new SRIF agonist, pasireotide, displaying a broader receptor-binding profile compared with octreotide and lanreotide, appears promising for the medical treatment of Cushing’s disease (Ben-Shlomo & Melmed 2007).

The item becomes even more interesting when we are faced with the plurihormonal adenomas of the acidophilic cell line, namely the pure somatotroph, somatomammotroph tumours, the truly mixed GH/PRL adenomas and even the very rare stem cell tumour (Asa et al. 1992). This assorted family represents the 30% of pituitary tumours in acromegaly. The plurihormonal adenomas have been shown to be functionally different, displaying a different sensitivity to the treatment with SRIF and/or DA agonists, also when administered in combination. Indeed, although the target cell could contribute to drug sensitivity, again in this case the specific receptor distribution on tumour cells plays the major role in determining the sensitivity to both SRIF and DA analogues (Ferone et al. 2001). In fact, it has been recently demonstrated that the really mixed GH/PRL tumours seem more resistant to SRIF analogues, whereas almost no difference in sensitivity, not only to SRIF analogues but also to DA agonists, has been observed in somatotroph and somatomammotroph adenomas (Ferone et al. 2008). This seems to be mainly due to the lower density of sst2 in mixed tumours. However, an interfering role of other receptor subtypes cannot be ruled out. Indeed, previously, in an
experimental model, a full concordance between tumour response to the DA agonist bromocriptine and the expression of D2 receptors by tumour cells was found in five lineages of a spontaneous transplantable rat pituitary tumour (SmTTW) exhibiting different PRL/GH phenotypes (Trouillas et al. 1999). This model resembles the various tumour phenotypes encountered in human pituitary pathology. However, Zatelli et al. (2005) elegantly investigated the in vitro response of a heterogeneous group of human somatotroph adenomas to experimental SRIF analogues. The authors suggested that adenomas expressing D2 are less likely to respond to SRIF analogues in terms of inhibition of GH secretion (Zatelli et al. 2005).

The modern view of the concept of resistance to medical therapy must take into account the effect on tumour mass as well. Indeed, until a few years ago, in secreting adenomas, the responsiveness or resistance to the medical therapy was defined according to the hormonal response. In general, the cases biochemically responsive were those experiencing also significant tumour size reduction during long-term treatments. However, at least for somatotroph adenomas treated with SRIF analogues, it is becoming clear that many adenomas may undergo impressive tumour shrinkage, although the hormonal hyperproduction is not fully controlled (Bevan 2005, Casarini et al. 2006, Cozzi et al. 2006, Resmini et al. 2007).

To overcome the resistance to single-agent treatment, the use of a combined SRIF analogue and DA agonist treatment schedule has been explored, particularly in GH-secreting adenomas, which are known to be potentially responsive to both classes of compounds (Colao et al. 2007). More recently, NFPAs were shown to be sensitive to a combined treatment as well, however, the response rate seems limited (Colao et al. 2007). No study with combined therapy has been reported in PRL- and ACTH-secreting adenomas so far, and no rationale exists today for such an approach with the presently available compounds (Table 1).

The emerging concept of somatostatin and D2 dopamine receptors dimerisation in pituitary adenomas: implications for pharmacology and drug discovery

The experience of combination therapy has paved the way for new studies that have provided the first evidence for a new challenge in the field of receptor pathophysiology and therapeutic strategies. Indeed, the discrepancy between the ‘presence’ of a given profile of SSR/D2 and the limited efficacy of agonist drugs may be partially explained by the crosstalk on the cell membranes, or even at post-membrane level, of the GPCRs (Ferone et al. 2007b, Saveanu & Jaquet 2008). The preclinical use of new experimental compounds is crucial for understanding the new picture. In fact, SSR distinct profiles may correspond to different responses to SRIF subtypes preferential ligands. For example, the sst5 preferential ligand, BIM-23268, suppresses PRL secretion in prolactinomas, as well as ACTH secretion in corticotroph tumours (Saveanu & Jaquet 2008). The relationship between SSR expression and their functionality may be more complex in GH-secreting adenomas expressing low levels of sst2, where the sst2-preferential ligand octreotide is ineffective in suppressing GH release. In such cases, an sst5 selective agonist may be of value because this SSR subtype is

<table>
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<th>Author (years)</th>
<th>Dopamine agonist</th>
<th>Somatostatin analogue</th>
<th>Disease</th>
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<td>Lamberts et al. (1986)</td>
<td>BRC</td>
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R, review; BRC, bromocriptine; CAB, cabergoline; OCT, octreotide; LAN, lanreotide; CV, quinagolide; NFPA, clinically non-functioning pituitary adenoma.
often highly expressed (Saveanu et al. 2001). However, in this specific setting, a bi-specific analogue, such as BIM-23244, which can activate both receptors, could achieve a better control of GH hypersecretion (Saveanu et al. 2001). Moreover, a selective sst1 ligand, BIM-23926, has been shown to inhibit in vitro hormone secretion and cell viability in GH- and PRL-secreting adenomas and in a subset of NFPAs (Zatelli et al. 2003, 2004). Whereas in corticotroph adenomas, the predominant mRNA expression of sst5 over sst2 makes these adenomas highly sensitive to multireceptor ligands, such as the new SRIF analogue pasireotide (de Bruin et al. 2009). Recent data have showed that pasireotide modulates SSR trafficking in a manner clearly distinct from other SRIF analogues, providing an alternative explanation for the differential regulation of SSR responsiveness during long-term administration of stable SRIF analogues (Lesche et al. 2008). Moreover, SSRs act not just as monomers but may display a differential tendency to homo- and heterodimerise, depending on the subtype involved, and perhaps also on the cell type in which they are expressed (Durán-Prado et al. 2008). Indeed, pairs of distinct SSRs, such as sst2–sst3 and sst1–sst5, may interact and establish a physical interaction, resulting in altered pharmacological or/and functional properties (Durán-Prado et al. 2008).

In this view, while the first chemical approach, following the discovery of the five SSRs, was to construct ligands with a high affinity for each subtype, more recently the pharmaceutical companies have driven the research toward new compounds interacting with more than one SSR subtype. Moreover, knowing the association of SSRs and D2 receptor in the majority of pituitary adenomas, another chemical approach consisted in the synthesis of chimeric molecules containing structural elements of both SRIF and DA and directed against both the superfamilies of GPCRs (Ferone et al. 2007a, b, Saveanu & Jaquet 2008). The first molecules of this class, BIM-23A387 and BIM-23A760, were characterised by their sst2 and D2 and sst2, sst5 and D2 affinity respectively, and resulted effective in controlling hormone hypersecretion in vitro in somatotroph adenomas that were partial responders to octreotide (Saveanu et al. 2006). These chimeric compounds were effective at lower concentrations compared with analogues directed toward a single receptor, and were even more efficient than octreotide in combination with cabergoline (Saveanu et al. 2006).

In addition to the binding properties of the hybrid compounds, other mechanisms may explain their greater efficiency in suppressing hormone release: the pharmacokinetics characteristics, the longer stability...
and, very intriguing, the demonstrated capacity in transfected cell lines, in which SRIF and DA ligands could induce or maintain receptor homo- and heterodimerisation and increase functional activity (Rocheville et al. 2000). This latter observation suggests that at least a portion of the high activity of these chimeric molecules may be due to promoting the formation of dimers between GPCRs.

Presently, the experience with the so-called ‘dopastatin’ molecules has been extended to the NFPA as well (Gruszka et al. 2006, Ferone et al. 2007b, Florio et al. 2008). Although in vitro chimeric agonists were effective in inhibiting z-subunit secretion (Ferone et al. 2007b) as well as cell proliferation (Florio et al. 2008) in this heterogeneous class of pituitary tumours, the results appear less convincing so far. From a certain point of view, it seems that also the chimeric molecules may act differently in various tissues tested, and the effect could differ according to cell types. Actually, this hypothesis was already explored with SSR subtype-specific analogues. In fact, another in vitro study on NFPA, while revealing the potential importance of sst1 in mediating an inhibitory effect of a selective agonist on chromogranin A and z-subunit secretion as well as on cell viability, also demonstrated that the incubation of these cells with a sst2-selective agonist may enhance pituitary cell viability (Zatelli et al. 2004). Therefore, it seems that the coexpression of SRIF and D2 receptors is not sufficient to improve the responsiveness of pituitary tumours to the anti-secretory and/or the anti-proliferative actions of the new class of hybrid compounds, indicating that once again the cell type should also be taken into account. In support of this hypothesis is the experience in testing these drugs with other cell systems than pituitary cells. For example, dopastatins resulted more effective in inhibiting cell growth in a non-small lung carcinoma cell line compared with subtype-specific SSR analogues and DA agonists, demonstrating in this cell system, constitutively expressing SSRs and DRs, a clear additivity of the hybrid compounds (Ferone et al. 2005). Conversely, in gastric enterochromaffin-like cell, the dopastatin BIM-27A760 did not displayed an additive effect on histamine secretion and cell proliferation (Kidd et al. 2007). On the other hand, the activation of multiple SSRs by pasireotide significantly reduced cell proliferation in the neuroendocrine tumour cell line NCI-H727 (Ono et al. 2007), and inhibited cell growth and catecholamine secretion in cell cultures of phaeochromocytoma, also inducing apoptosis (Pasquali et al. 2008). Indeed, a differential cytotoxicity of chimeric compounds was recently observed in bronchopulmonary and small intestinal neuroendocrine tumour cell lines (Kidd et al. 2008). The responses of each individual cell line suggested that neuroendocrine tumours from diverse locations arising from different neuroendocrine cells may require cell-specific anti-proliferative agents based on the unique receptor profile of individual lesions (Kidd et al. 2008). Pituitary and ectopic corticotroph tumours, expressing sst2, sst5 and D2 receptors, are promising potential target for dopastatin molecules. In fact, although up to now no data have been issued in this field, pre-clinical results and single preliminary clinical experiences encouraged the research in this group (Pivonello et al. 2005, de Bruin et al. 2009), while in prolactinomas, where sst2 and D2 are coexpressed, only a slight additivity of specific agonists was demonstrated in cell cultures (Saveanu & Jaquet 2008).

Finally, GPCR dimerisation seems to influence not only pituitary cell functions, but may also provide a mechanism for the lack of tolerance seen with currently available SRIF analogues and their ability in controlling pituitary tumour growth. Indeed, heterodimerisation between sst2 and sst5 has been recently found involved in this important phenomenon (Grant et al. 2008). The next important step will be the accurate characterisation of the post-receptor signalling pathways, which certainly depend on the SRIF and DR profile; however, it could be significantly affected by the specific neuroendocrine (and non-neuroendocrine) cell type (Fig. 3).

In conclusion, the lack of clinical response of a rather high percentage of patients with pituitary adenomas to the currently available drugs could be due not only to an inadequate characterisation of the pituitary tumour receptor profile, but also to the fact that a sort of cell specificity in the response may affect the final outcome. Moreover, in this scenario, we should also consider the new insight of receptor dimerisation. Dimerisation is fairly common in the GPCR superfamily, and overwhelming amounts of data suggest that many GPCRs, including SSRs and DRs, exhibit functional properties that require direct or indirect interactions between clustered receptors. The integration of this property of the SSRs and DRs in the know-how is crucial to elucidate the physiological mechanism of action of certain hormones, while an understanding of the mechanisms involved in these events could offer a rationale in next drug design, also for tumours arising from other cells expressing GPCRs.

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this work.

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