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# Relevance of coexpression of somatostatin and dopamine D2 receptors in pituitary adenomas

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**Abstract**

Dopamine and somatostatin are both involved in the negative control of normal pituitary cells. Dopamine subtype 2 receptor (D2DR) and somatostatin receptor (sst) agonists, mainly directed to sst2, are used in the treatment of pituitary adenomas. Nevertheless, a majority of corticotroph and gonadotroph adenomas and a third of somatotroph adenomas are still not sufficiently controlled by these treatments. D2DR and sst1, 2, 3 and 5 are present in most pituitary adenomas. These receptors may interact by heterodimerization as shown for sst1–sst5, sst5–D2DR, sst2–sst3 and sst2–D2DR suggesting possible additive effects. D2DR and sst2 agonist cotreatment showed limited additivity on GH secretion in acromegaly. Moreover, new chimeric compounds with sst2, D2DR and sst5 affinity have shown an increased control of secretion and/or proliferation of different types of pituitary adenomas in cell culture. Together with the multi-sst ligand drugs recently developed, these dopamine–somatostatin ligands represent a new opportunity in the combinatory treatment of pituitary adenomas.


*Keywords:* Somatostatin; Dopamine; Pituitary adenomas; sst2; sst5; D2DR; Dopastatin; Heterodimerization

## 1. Introduction

Depending on the point of view that is considered, different target audiences will find coexpression of somatostatin receptors (sst) and dopamine subtype 2 receptors (D2DR) in pituitary adenomas relevant for distinct reasons: clinicians are mainly interested in the potential therapeutic use of the cooperation of various receptor subtypes, while basic researchers are more eager to decipher the mechanisms whereby such a cooperation may occur. These are the topics that we will briefly address in the present review with reference to the most recent findings in the field.

## 2. sst and D2DR in pituitary adenomas

Both somatostatin and dopamine are neurohormones implicated in the negative control of hormonal secretion of the anterior pituitary gland (Guillemin, 2005; Ben-Jonathan and Hnasko, 2001). They act through binding to membrane receptors: G protein coupled receptors (GPCR) that are present on the cells of the normal pituitary: somatostatin receptor subtypes 1, 2, 3 and 5 (Miller et al., 1995; Panetta and Patel, 1995; Batista et al., 2006; Thoss et al., 1996) and D2DR (Mansour et al., 1990). Pituitary tumors are mostly benign tumors derived from different pituitary cell types that retain most of the characteristics of the original cells (Asa and Ezzat, 1998). Accordingly sst subtypes 1, 2, 3 and 5 and D2DR were found to be present in a majority of pituitary adenomas, irrespective of their type (reviewed in Moller et al., 2003; Stefaneanu et al., 2001). The interstudy variability is reflecting both a different sensitivity of the techniques used and a huge heterogeneity of these adenomas. However, like others (Panetta and Patel, 1995; Nielsen et al., 1998; Taboada et al., 2007; Schaer et al., 1997), we found in most GH adenomas (Jaquet et al., 2000; Saveanu et al., 2002, 2006), sst2, sst5 and D2DR mRNA coexpression, in keeping with protein studies (Stefaneanu et al., 2001; Schaer et al., 1997; Reubi et al., 2001; Thodou et al., 2006) showing the same trend. Moreover half of GH tumors also disclosed sst3 and sst1 coexpression.

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The latter is present mainly in mixed GH and PRL adenomas (Jaquet et al., 2000). Indeed, in prolactinomas, sst1, sst5, sst2 and of course D2DR are present (Miller et al., 1995; Panetta and Patel, 1995; Stefaneanu et al., 2001; Taboada et al., 2007; Thodou et al., 2006; Jaquet et al., 1999; Caccavelli et al., 1994). Nonfunctioning pituitary adenomas (NFPA), that are mostly of gonadotroph origin, express sst2, sst3 (Nielsen et al., 1998; Taboada et al., 2007; Reubi et al., 2001; Saveanu et al., 2001a; Zatelli et al., 2004) and D2DR (Stefaneanu et al., 2001; Pivonello et al., 2004a), seldom associated with sst1 (Taboada et al., 2007). Corticotroph adenomas mainly express sst5, sst2 (Miller et al., 1995; van der Hoek et al., 2005) and D2DR (Stefaneanu et al., 2001; Pivonello et al., 2004b) and less frequently sst1 and sst3 (Miller et al., 1995; Panetta and Patel, 1995; Batista et al., 2006). The least frequent pituitary adenomas, TSH adenomas, express sst1, sst2 and sst5 (Panetta and Patel, 1995; Murabe et al., 1996; Yoshihara et al., 2007) and D2DR receptors ((Stefaneanu et al., 2001) and personal unpublished data). Despite a great variability in the techniques from one study to another (Northern Blot, quantitative-PCR, radioactive binding studies or immunohistochemistry), D2DR expression is overall associated with two or more sst subtypes in most tumors with some patterns: sst2 + sst5 in GH adenomas, sst3 + sst2 in NFPA or sst1 + sst5 in prolactinomas. Such observations however did not always correlate with the efficacy of the corresponding drugs. Indeed, while D2DR agonists are efficient in treating more than 90% prolactinomas (reviewed in Molitch, 2005; Colao et al., 2006), somatostatin analogs clinically in use (Octreotide and Lanreotide) only control about 80% of TSHoma (Socin et al., 2003; Caron et al., 2001) and 60% of GH adenomas (reviewed in Freda, 2002). Moreover, sst or D2DR agonists control less than 20% of NFPA adenomas (reviewed in Chanson and Brochier, 2005) and even fewer corticotroph adenomas (Pivonello et al., 2004b; Lamberts et al., 1989; Stalla et al., 1994). This discrepancy between the "presence" of sst and D2DR receptors and the partial efficacy of agonist drugs needs to be explained.

## 3. Why do current sst and D2DR agonists only partially control pituitary adenomas?

Clinically used somatostatin analogs, octreotide and lanreotide, have sst subtype affinities, that are clearly different from those of native somatostatin (SRIF14) (see Table 2). They have a good sst2 affinity, while sst5 affinity is lower than that of SRIF14 (the ratio of sst2 and sst5 affinities being about 12 for octreotide and 18 for lanreotide). Octreotide also has some sst3 affinity; about 25 times lower than that of SRIF14. Both drugs do not recognize sst1 and sst4 subtypes. sst4 is not or is weakly expressed in pituitary and the functions of sst3 in pituitary remains unclear. However, sst5 subtype could be an important actor in suppressing GH, ACTH and PRL secretion from human pituitary adenomas (Jaquet et al., 1999; van der Hoek et al., 2005; Shimon et al., 1997), while sst1 subtype also may suppress the secretion or the viability of GH, prolactin and gonadotroph adenoma cells *in vitro* (Zatelli et al., 2003,2004; Matrone et al., 2004). So, octreotide and lanreotide do not cover all the sst subtypes able to suppress secretion and proliferation of different pituitary adenoma cell types.

Furthermore, the level of expression of sst subtypes and D2DR is an important factor of agonist action. According to our experiments in GH tumors (Jaquet et al., 2005a), as measured by real-time quantitative-PCR, sst2 mRNA ranged from 0.01 to 3 copy sst2/copy β Gus. Other recent studies using this technique found a similarly wide range of mRNA expression (Taboada et al., 2007). Such a wide range of sst2 expression levels explains, at least partially, the variability of GH suppression by octreotide and lanreotide in acromegalic patients. Indeed, the *in vitro* or *in vivo* octreotide sensibility is correlated with sst2 mRNA levels in somatotroph tumors (Jaquet et al., 2000; Saveanu et al., 2001b; Barlier et al., 1999). Similarly, D2DR quantitative detection showed a wide range of D2DR mRNA amounts, ranging from 0.01 to 15 copy/copy βgus (Saveanu et al., 2006) and GH or PRL suppression under D2DR agonists was correlated to D2DR levels in lactotroph and somatotroph tumors *in vitro* (Saveanu et al., 2006; Pellegrini et al., 1989). In gonadotrophinomas, octreotide was found to be less efficacious than in somatotroph adenomas, probably also because sst2 mRNA expression is 20 times lower than in GH tumors (Saveanu et al., 2001a,b). However, the efficacy of octreotide is not always 100% correlated to the sst2 expression level. Other mechanisms can be involved in drug resistance, like defects downstream of the receptors. This was clearly shown for D2DR in resistant prolactinomas (Pellegrini et al., 1989; Caccavelli et al., 1996; Barlier et al., 1997).

## 4. Hopes for new treatments

Thus, if the expression amount of target receptors is a crucial parameter for the response level to specific agonists (sst2 for octreotide and D2DR for cabergoline), how could this limitation be overcome?

The simplest solution is to simultaneously activate several types of inhibitory receptors in order to obtain an additive effect on secretion and proliferation. Clinicians had already tried empirically this option, in somatotroph adenomas (reviewed in Colao et al., 2007) or in NFPA (Andersen et al., 2001) by co-administration of the available sst2 (octreotide/lanreotide) and D2DR analogs (bromocriptine, cabergoline, quinagolide). Most of these studies showed some additivity between both drugs but the overall results were modest. For example, in one of the latest and most optimistic studies in acromegaly, co-administration of cabergoline and somatostatin analogs slightly improved the control of GH secretion from mean GH values of 6.6 to an average of 4.6 ng/ml (Cozzi et al., 2004).

Two kinds of *in vitro* experiments have successively raised new hopes:

The first one concerns a new actor: sst5. This sst subtype is present in most GH, PRL and ACTH tumors. Drugs with selective affinity for sst5 were able to suppress GH and ACTH secretion from human pituitary adenomas *in vitro* (van der Hoek et al., 2005; Shimon et al., 1997). Moreover, the combination of sst5 specific drugs with sst2 specific agonists showed an improvement of GH suppression in about half of