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Distinct functional properties of native somatostatin receptor subtype 5 compared with subtype 2 in the regulation of ACTH release by corticotroph tumor cells

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Cushing's disease; adrenocorticotropic hormone; glucocorticoid

CUSHING'S DISEASE, the pituitary-dependent form of Cushing's syndrome, is the hypercortisolemic state secondary to excess or dysregulated ACTH secretion caused by an ACTH-secreting pituitary adenoma (36). The significant associated morbidity, such as increased tissue fragility, poor wound healing, hypertension, and diabetes mellitus, demands a proper medical intervention (1). Transsphenoidal surgery is currently the first line of treatment, and secondary options consist of irradiation therapy either alone or in combination with adrenolytic agents (10, 34, 35, 37). Unfortunately, none of the current treatment modalities ensures a full and permanent cure, as evidenced by the number of patients developing recurrent Cushing's disease (43). The absence of an effective medical treatment has prompted physicians to explore new medical strategies, preferably based on fundamental and (patho)physiological pathways, in the hope of increasing the curation chances in this group of patients.

The physiological role of somatostatin (SS) in the regulation of anterior pituitary function (5, 27, 41, 45), its equivocal effects on ACTH release (6, 24), and the current use of SS analogs in patients with anterior pituitary tumors (29), has led to the exploration of SS analogs in patients with (recurrent) Cushing's disease. To date, five G protein-coupled SS receptors have been cloned (sst_1–sst_5), and six gene products are currently known (39, 45). The receptor subtypes $sst_{1–5}$ produce single gene products, whereas sst_{2A} (long form) and sst_{2B} (short form) originate from a common precursor mRNA, which is spliced at the carboxyl terminus (56). Although in vitro data demonstrate the presence of sst expression in corticotroph adenomas, the sst_2-preferential analog octreotide (OCT) appears to inhibit ACTH release in Nelson's syndrome and in some patients harboring ectopic ACTH-producing tumors, but rarely in patients with Cushing's disease (13, 30). These observations are in agreement with the observation that almost all ACTH-secreting pituitary adenomas, i.e., patients with untreated Cushing's disease, cannot be visualized by SS receptor (sst) scintigraphy using ^{111}In-diethylenetriamine pentaacetic acid (DTPA) OCT (12, 28), whereas ^{111}In-DTPA scintigraphy is positive in patients with Nelson's syndrome (11, 12). Apparently, ACTH release from corticotropinomas is sensitive to OCT only in the absence of peripheral feedback regulation by glucocorticoids, suggesting that the sst_2 might be downregulated when cortisol levels are high. Additional in vitro evidence for this hypothesis comes from studies using primary

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