Somatostatin (SRIF) is a 14 amino-acid-containing peptide primarily expressed in the hypothalamus. It is a major physiological regulator of growth hormone (GH) secretion and is critical in maintaining the pulsatile release of GH. SRIF induces its biological effects by interacting with membrane-associated receptors, of which a family of five have recently been cloned. The cloned receptor subtype referred to as sstr2 may have an important role in mediating the inhibitory effects of SRIF on GH secretion. This is suggested from pharmacological studies showing that a large series of SRIF analogs, including the clinically used peptides octreotide and lanreotide, had a similar rank order of affinities for binding to sstr2 and to inhibit GH secretion. Stimulation of sstr2 may lead to inhibition of Ca\textsuperscript{2+} influx into somatotrophs to reduce GH secretion. Structural analysis of the cloned sstr2 has revealed binding domains of the receptor that may be useful in the development of antagonists and nonpeptide agonists at this receptor, which could have clinical uses in the regulation of GH secretion and other biological functions of SRIF.
INTRODUCTION

SRIF is an important regulator of GH secretion from the anterior pituitary (1). The effects of SRIF are mediated directly at the level of the pituitary and are also mediated via feedback loops in the hypothalamus. The peptide has other physiological actions. It is secreted from delta cells of the pancreas to inhibit insulin and glucagon release and has a role in regulating amylase and gastric acid secretion. SRIF is also a neuromodulator in the brain involved in regulating locomotor activity and cognitive functions.

In addition to SRIF, a larger precursor, somatostatin-28 (SRIF 28) is also expressed in the body and like SRIF can regulate hormone and neurotransmitter release. Pharmacological studies have even suggested that SRIF and SRIF 28 may have some different primary biological roles; since SRIF 28 was reported to be more potent than SRIF in controlling insulin release whereas it was equipotent with SRIF in control glucagon secretion (2). Furthermore, SRIF 28 is the predominant somatostatin peptide expressed in the gastrointestinal tract, suggesting a primary role of the peptide in controlling gastric-acid secretion. In contrast, SRIF is primarily expressed in the hypothalamus and may subserve a more essential role than SRIF 28 in regulating GH secretion.

Recently, a third somatostatin-like peptide was identified, cortistatin (3). This peptide has a somewhat similar structure to SRIF, but is derived from a different prohormone. This peptide is able to induce some similar actions as SRIF and can bind to the same receptors as SRIF. However, it is also able to induce distinct actions from SRIF, in particular effects on slow-wave sleep. This latter finding suggests that cortistatin may be able to interact with a different receptor than SRIF.

SRIF RECEPTOR SUBTYPES

SRIF induces its biological actions by interacting with membrane-associated receptors. A number of studies had suggested that subtypes of SRIF receptors are expressed in the body (1). Studies on the pancreas suggested that SRIF 28 was much more potent than SRIF in blocking insulin secretion, whereas the peptides had similar potencies in controlling glucagon release (2), indicating that different receptors may be involved in mediating SRIF peptide effects on pancreatic hormone secretions. Receptor binding studies suggested that radiolabeled SRIF analogs bound to multiple sites in different tissue preparations (4). Synthetic peptides such as octreotide and MK 678 bound potently to one site and not the other. Furthermore, one binding site was sensitive to guanine triphosphate (GTP) analogs and Na⁺ whereas the binding of SRIF to the other site was not. In addition, antibodies made against native SRIF receptors revealed heterogeneities in the size of SRIF receptors, which are likely to be owing to the antibodies being raised against different receptor subtypes (5).

Cloning of SRIF Receptors

The cloning of a family of SRIF receptors confirmed that subtypes of these receptors exist and are expressed in the body (1,6). Bell and his associates (7,8) cloned the first three SRIF receptors and named them sstr1, sstr2, and sstr3. Berelowitz and his associates (9) cloned the fourth receptor and O’Carroll (10) cloned the fifth receptor. The five