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Biological activity of somatostatin receptors in GC rat tumour somatotrophs: evidence with sst₁–sst₅ receptor-selective nonpeptidyl agonists

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Abstract

The physiological actions of somatostatin-14 (SRIF: somatotrophin release inhibitory factor) receptor subtypes (sst₁–sst₅), which are endogenously expressed in growth cells (GC cells), have not yet been elucidated, although there is evidence that sst₂ receptors are negatively coupled to cytosolic free Ca²⁺ concentration ([Ca²⁺]_i) and adenosine 3',5'-cyclic monophosphate (cAMP) accumulation. In addition, both sst₁ and sst₂ receptors are negatively coupled to growth hormone (GH) secretion in GC cells. Here we report on studies concerning the expression, the pharmacology and the functional role of native SRIF receptors in GC cells with the use of five nonpeptidyl agonists, highly selective for each of the SRIF receptors. Radioligand binding studies show that sst₂ and sst₅ receptors are present at different relative densities, while the presence of sst₃ and sst₄ receptors appears to be negligible. The absence of sst₁ receptor binding was unexpected in view of sst₁ receptor functional effects on GH secretion. This suggests very efficient receptor–effector coupling of a low-density population of sst₁ receptors. Functionally, only sst₂ receptors are coupled to the inhibition of [Ca²⁺]_i and cAMP accumulation and the selective activation of sst₅ receptors facilitates the stimulation of adenylyl cyclase activity through G_{i/o} proteins. This effect was not observed when sst₂ and sst₅ receptors were simultaneously activated, suggesting that there is a functional interaction between sst₂ and sst₅ receptors. In addition, sst₁, sst₂ and sst₅ receptor activation inhibits GH release, further indicating that SRIF can modulate GH secretion in GC cells through mechanisms both dependent and independent on [Ca²⁺]_i and cAMP-dependent pathways. The present data suggest SRIF-mediated functional effects in GC cells to be very diverse and provides compelling arguments to propose that multiple native SRIF receptors expressed in the same cells are not simply redundant, but contribute to marked signalling diversity.

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1. Introduction

Somatostatin-14 (SRIF: somatotrophin release inhibitory factor) originally discovered as a hypothalamic inhibitor of growth hormone (GH) secretion, acts through at least five distinct heptahelical, G-protein-

coupled SRIF receptor subtypes (sst₁–sst₅; Benali et al., 2000). The action of SRIF receptor activation on both cytosolic free Ca²⁺ concentration ([Ca²⁺]_i) and adenosine 3',5'-cyclic monophosphate (cAMP) levels is critically relevant to SRIF's physiological role as an inhibitor of secretion (Patel, 1999). In particular, in rat somatotrophs, SRIF-induced inhibition of GH secretion is due, at least in part, to the inhibition of [Ca²⁺]_i and cAMP levels (Djordjijevic et al., 1998; Epelbaum et al., 1994; Lussier et al., 1991; Tomic et al., 1999b). The precise involvement of SRIF receptors in these effects is, however,

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