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ORIGINAL ARTICLE

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Somatostatin (SRIF) modulates distinct signaling pathways in rat pituitary tumor cells; negative coupling of SRIF receptor subtypes 1 and 2 to arachidonic acid release

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Abstract The somatotropin release-inhibiting factor somatostatin-14 (SRIF) is known to activate distinct receptor subtypes (sst_{1-5}). In rat pituitary tumor cells (GC cells), sst_2 but not sst_1 receptors mediate the SRIF-induced inhibition of intracellular concentration of Ca^{2+} ($[Ca^{2+}]_i$) and are negatively coupled to cAMP-dependent pathways. In the present study, transduction mechanisms coupling distinct SRIF receptors to their specific functional role were investigated with the use of both SRIF agonists with well-known affinity at individual SRIF receptors and the sst_2 receptor antagonist L-Tyr^8 isomer of Cyanamid 154806 (CYN-154806). Our results demonstrate that sst_1 and sst_2 receptors are coupled to distinct signaling pathways in GC cells. In particular, sst_2 receptors are negatively coupled to the cAMP-dependent pathway and this pathway is partially responsible for the sst_2 receptor-mediated inhibition of $[Ca^{2+}]_i$. In addition, sst_1 and sst_2 receptors are both coupled to a decrease of arachidonic acid (AA) release with an efficacy similar to that of SRIF, suggesting that SRIF reduces AA release through either a partial activation of both receptors or the activation of one at a time. This finding is important given the well-accepted role for phospholipase A_2 (PLA_2) as a positive signaling component in transduction pathways of SRIF receptors. sst_1 and sst_2 receptor negative coupling to PLA_2/AA pathways does not seem to be implicated in the SRIF-induced inhibition of $[Ca^{2+}]_i$. The possible role for the SRIF-mediated inhibition of AA release in GC cell function remains to be elucidated.

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Introduction

Rat pituitary somatotrophs exhibit spontaneous or stimulated electrical activity associated with transient increase of intracellular free calcium concentration ($[Ca^{2+}]_i$; Kwiecien et al. 1997; Tomic et al. 1999a). The $[Ca^{2+}]_i$ is critical in the control of both basal and stimulated growth hormone (GH) secretion (Tomic et al. 1999a, 1999b). Somatostatin-14 (somatotropin release-inhibiting factor; SRIF) is a naturally occurring hypothalamic tetradecapeptide (Brazeau et al. 1973) that inhibits rhythmic $[Ca^{2+}]_i$ transients (Kwiecien et al. 1997; Tomic et al. 1999b), thus reducing GH release from pituitary cells (Tomic et al. 1999b).

In many cell types, SRIF controls $[Ca^{2+}]_i$ by binding to one or more individual SRIF receptor subtypes, named sst_1–sst_5 receptors (for review see Patel 1999). In pituitary cells, the SRIF receptors mediating SRIF action on $[Ca^{2+}]_i$ transients are not well characterized, although an involvement of sst_1, sst_2 and sst_5 receptors in the SRIF-induced reduction of GH release has been demonstrated (Raynor et al. 1993; Briard et al. 1997; Shimon et al. 1997; Djordjijevic et al. 1998; Kreienkamp et al. 1999; Parmar et al. 1999).

Growth Cells (GC cells) belong to a cell line derived from a rat pituitary tumor (subclone of the GH_3 strain). In contrast to normal somatotrophs, they all exhibit spontaneous, rhythmic action potentials and concomitant oscillations of $[Ca^{2+}]_i$ (Kwiecien et al. 1998) which, in turn, allow GH secretion. This process is inhibited by the application of octreotide, a long-lasting SRIF agonist (Mounier et al. 1995) that displays high affinity for sst_2 receptors, although it also binds to sst_5 receptors (Raynor et al. 1993; Siehler et al. 1998; Siehler and Hoyer 1999). Previous results have demonstrated that the membranes of GC cells express distinct SRIF receptors and, in particular, sst_1 and