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ORIGINAL ARTICLE

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Somatostatin coupling to adenylyl cyclase activity in the mouse retina

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Abstract The peptide somatostatin-14 (SRIF) acts in the mammalian retina through its distinct receptors (sst_{1-5}). Scarce information is available on SRIF function in the retina, including the elucidation of transduction pathways mediating SRIF action. We have investigated SRIF and SRIF receptor modulation of adenylyl cyclase (AC) activity in both wild-type (WT) retinas and sst_1 or sst_2 knock-out (KO) retinas, which are known to over-express sst_2 or sst_1 receptors respectively. In WT retinas, application of SRIF compounds does not affect forskolin-stimulated AC activity. In contrast, activation of sst_1 or sst_2 receptors inhibits AC in the presence of sst_2 or sst_1 receptor antagonists respectively. Results from sst_1 KO retinas demonstrate that either SRIF or the sst_2 receptor preferring agonist octreotide, pertussis toxin-dependently inhibit AC activity. In contrast, in sst_2 KO retinas, neither SRIF nor CH-275, an sst_1 receptor agonist, are found to influence AC activity. As revealed by immunoblotting experiments, in sst_1 KO retinas, levels of $G_o\alpha$ proteins are 60% higher than in WT retinas and this increase in $G_o\alpha$ protein levels is concomitant with an increase in sst_{2A} receptor expression. We conclude that interactions between sst_1 and sst_2 receptors may prevent SRIF effects on AC activity. In addition, we suggest that the density of sst_2 receptors and/or $G_o\alpha$ proteins may represent the rate-limiting factor for the sst_2 receptor-mediated inhibition of AC.

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Introduction

Somatostatin-14 (somatotropin release-inhibiting factor, SRIF) is a neuropeptide widely distributed in the mammalian nervous system. SRIF exerts its functions by interacting with plasma membrane receptors. Five G protein-coupled SRIF receptors have been cloned and termed sst_1 through sst_5 receptors (Weckbecker et al. 2003).

Somatostatin-14 and its receptors are also found in the mammalian retina (Bagnoli et al. 2003). In the mouse retina, for instance, sparse-occurring amacrine cells contain SRIF and express sst_1 receptors (Cristiani et al. 2002; Dal Monte et al. 2003b). Specific binding for sst_2 receptors has been also shown in the mouse retina (Dal Monte et al. 2003b). In particular, of the two sst_2 receptor isoforms (sst_{2A} and sst_{2B}), the sst_{2A} isoform is expressed by rod bipolar, by horizontal and by amacrine cells including dopaminergic amacrine cells (Cristiani et al. 2002; Dal Monte et al. 2003a, 2003b). The sst_{2B} isoform has been localised by Vasilaki et al. (2001) to photoreceptor outer segments in the rat retina in which, on the other hand, Johnson et al. (1999) have not detected sst_{2B} receptor mRNA. Finally, the sst_4 receptor is in sparse ganglion cells of the mouse retina, whereas low to very low levels of sst_3 and sst_5 receptor mRNAs were detected (Cristiani et al. 2002).

Although possible involvement of SRIF in retinal diseases has become recent interest (Thermos 2003), only little information is available on SRIF function in the retina. Findings to date suggest that SRIF acts on multiple retinal circuits to produce long-lasting changes in ganglion cell activity and receptive field organisation (Zalutsky and Miller 1990). There is also evidence indicating that SRIF modulates the physiology of retinal cells through the activation of its distinct receptors (Bagnoli et al. 2003). In