

Expression, pharmacology, and functional role of somatostatin receptor subtypes 1 and 2 in human macrophages

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Abstract: Somatostatin (SRIF)-14 is recognized as an important mediator between the nervous and the immune system, although the functional role of its receptors (sst_1 – sst_5) is poorly understood in humans. In our study, we demonstrate that human macrophages, differentiated from PBMC-derived monocytes, express sst_1 and sst_2 mRNAs. sst_1 and sst_2 are mostly localized at the cell surface and display active binding sites. In particular, $\text{sst}_1/\text{sst}_2$ activation results in a weak internalization of sst_1 , and the sst_2 internalization appears more efficient. At the functional level, the activation of SRIF receptors by the multiligand analogs SOM230 and KE108, but not by SRIF-14 or cortistatin-14, reduces macrophage viability. Their effects are mimicked by the selective activation of sst_1 and sst_2 using CH-275 and SMS 201-995/L-779,976, respectively. Further, sst_1 - and sst_2 -mediated effects are reversed by the sst_1 antagonist SRA-880 or the sst_2 antagonist CYN 154806, respectively. CH-275, SMS 201-995, and L-779,976, but not SRIF-14, decrease mRNA expression and secretion of the MCP-1. In addition, SRIF-14, CH-275, SMS 201-995, and L-779,976 decrease IL-8 secretion, and they do not affect IL-8 mRNA expression. In contrast, SRIF-14 and $\text{sst}_1/\text{sst}_2$ agonists do not affect the secretion of matrix metalloproteinase-9. Collectively, our results suggest that the SRIF system, through sst_1 and sst_2 , exerts mainly an immunosuppressive effect in human macrophages and may, therefore, represent a therapeutic window that can be exploited for the development of new strategies in pharmacological therapy of inflammation. *J. Leukoc. Biol.* 81: 845–855; 2007.

Key Words: neuropeptides · monocytes · trafficking · cell viability · chemokines · metalloproteinases

INTRODUCTION

The complex network of communication between the nervous and the immune system has become the subject of intense research in recent years. To maintain the function of the neuroimmune circuitry, cells in both systems produce diverse

chemical messengers, which are involved in the regulation of immunological and inflammatory responses [1]. In particular, cytokines and neuropeptides, which exist in the nervous and immune system, are potential mediators of cross-talk between the two systems. There is evidence to suggest that the circulating neuropeptide somatostatin (SRIF)-14, acting through its specific G protein-coupled receptors (sst_{1-5}) [2, 3], is one such mediator and may represent an important regulator of the immune response [4, 5]. For example, SRIF-14 has potent, modulatory actions on the release of Igs and cytokines. Furthermore, the peptide is also involved in inhibition of chemotaxis, phagocytic activity, and the NK cell activity of immune cells. In this respect, the synthetic SRIF analog TT232 has recently become a therapeutic candidate with anti-inflammatory indications and is currently under evaluation in clinical trials [6].

Monocytes and macrophages are recognized as important components of innate and acquired immunity. In rodent cells of the monocyte lineage, the inhibitory role of SRIF-14 has been studied extensively [7–14]. However, in human monocytes, the role of SRIF-14 is less well-understood, and reported results have been controversial [5, 15]. Human monocytes derived from PBMC do not express mRNA for SRIF-14 [16–18], and they do express the mRNA for cortistatin [16, 17], a SRIF-14-like peptide, which may serve as an alternative ligand for SRIF receptors in the immune system [19, 20]. The presence of SRIF receptors in monocytes has been suggested from binding studies [4, 5]. In addition, sst_2 mRNA has been observed in PBMC-derived monocytes [17]; however, this expression was undetectable under basal conditions and required cell activation to up-regulate the mRNA to a level that could be detected [15]. Circulating monocytes are versatile precursor cells with the ability to differentiate into various forms of specialized macrophages [21, 22], a process that is influenced profoundly by the cytokine milieu. The functional activation of macrophages can occur by “classical” or “alternative” activators, resulting in functionally polarized cells [23, 24]. The activation of macrophages by LPS is considered a

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Received June 28, 2006; revised September 20, 2006; accepted November 5, 2006.

doi: 10.1189/jlb.0606417