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Binding and functional properties of the novel somatostatin analogue KE 108 at native mouse somatostatin receptors

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Abstract

Clinically used somatostatin (SRIF) analogs, octreotide and lanreotide, act primarily by binding to SRIF receptor subtype 2 (sst_2). In contrast, the recently described multiligand SOM230 binds with high affinity to sst_{1-3} and sst_5 and KE 108 is characterised as a high affinity ligand for all five SRIF receptors. In tumoural mouse corticotrophs (AtT-20 cells) and in mouse hippocampus, binding and functional features of KE 108 were examined and compared to SRIF-14, octreotide and SOM230. In AtT-20 cells, KE 108 bound with high affinity at [^{125}I]LTT-SRIF-28-labelled sites similarly to SRIF-14, octreotide and SOM230. At the functional level, all four ligands increased guanosine-5′-*O*-(3-[^{35}S]thio)-triphosphate binding and decreased cAMP accumulation or intracellular Ca^{2+} concentration through $G_{i/o}$ proteins. In hippocampal slices, KE 108, octreotide and SOM230 also bound with high affinity at [^{125}I]LTT-SRIF-28-labelled sites similarly to SRIF-14, but KE 108, octreotide or SOM230 did not influence spontaneous epileptiform activity which was, in contrast, inhibited by SRIF-14. In conclusion, this study demonstrates that KE 108 has high affinity for native mouse SRIF receptors. Functionally, KE 108 mediates SRIF action at $sst_{2/5}$ in corticotrophs whereas it does not mimic the SRIF-induced inhibition of hippocampal excitation suggesting that the high potency and efficacy of a synthetic ligand to all known SRIF receptors may not reproduce entirely the effects of the natural SRIF.

Keywords: Somatostatin agonists; AtT-20 cells; Mouse hippocampus; Receptor binding; cAMP; Ca^{2+} regulation; Epilepsy

1. Introduction

Somatostatin (SRIF: somatotropin-release inhibiting factor) is a cyclic peptide that exists in two biologically active forms, SRIF-14 and SRIF-28, which have been linked to a number of pathologies, e.g. acromegaly, gastrointestinal disorders, tumours in addition to various psychiatric or neurological diseases, e.g. epilepsy, depression, schizophrenia and dementias. SRIFs are predominantly produced by normal endocrine, gastrointestinal and immune cells, as well as by certain tumours (Weckbecker et al., 2003). SRIFs are also present in numerous neuronal cells throughout the brain, including the hypothalamus and the hippocampal formation (Binaschi et al., 2003; Olias et al., 2004). SRIF actions are mediated by five receptors (sst_{1-5}) that are coupled to G proteins, and trigger multiple transmembrane signalling systems (Lahlou et al., 2004).

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