Michael Crider

Southern Illinois University Edwardsville, USA

Development of Somatostatin Subtype 4 (SST4) agonists for potential use in Alzheimer's disease

Somatostatin (SST) occurs in two biologically active forms SST-14 and a N-terminally-extended form SST-28. SST exerts its effects by binding to a family of G protein-coupled receptors designated sst1-sst5. Structure-activity studies have shown that the tetrapeptide fragment, Phe7-Trp8-Lys9-Thr10, comprises the critical β-turn of SST. Although Phe7 and Thr10 can be modified, Trp8 and Lys9 are essential for biological activity. Since nonpeptide SST ligands offer therapeutic advantages over peptides, a screening program was initiated to identify a nonpeptide SST ligand with affinity for sst1-sst5. The search focused on the following: An aromatic moiety to mimic Phe7; a heteroaromatic nucleus to mimic Trp8, and a primary amine or other basic group to mimic Lys9. Using these search criteria, NNC 26-9100 was identified as the first sst4 agonist having high affinity (Ki=6 nM) and 100-fold sst4/sst2 selectivity at cloned human sst4 receptors. In a forskolin-induced cAMP assay, NNC 26-9100 potently inhibited cAMP accumulation and was shown to be a full agonist. NNC 26-9100 increased the expression of the enzyme neprilysin in the SAMP8 mouse model of Alzheimer's disease. Neprilysin is the major Aβ-42 peptide degrading enzyme in the brain. Our studies demonstrate that NNC 26-9100 reduces Aβ-42 peptide levels in mouse cortex and that this reduction is associated with increased expression of neprilysin. Acute and chronic administration of NNC 26-9100 also increased learning and memory in SAMP8 mice using the T-maze test. These results suggest that NNC 26-9100 is a disease-modifying agent with potential use in the treatment of Alzheimer's disease. Current studies in our laboratory are focused on the discovery on novel heterocyclic scaffolds with high affinity and selectivity at sst4 receptors.

Speaker Biography

Michael Crider is Professor and Chair of the Department of Pharmaceutical Sciences at the School of Pharmacy at Southern Illinois University Edwardsville. Prior to assuming his present position, he held faculty positions at the University of Toledo and the University of Louisiana at Monroe. He has directed the research of 19 MS and PhD students. The focus of his research is in the design and synthesis of anticonvulsants, dopaminergics, and nonpeptide somatostatin agonists.

e: mcrider@siue.edu

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