IS01-2 The σ1 receptor as target for the development of novel drugs

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Originally the opioid receptor was subclassified into three subtypes, which were termed after their prototypical ligands μ (morphine), κ (ketocyclazocine) and σ receptors (SKF-10,047). However, this hypothesis was disproved, since the pharmacological effects of typical σ receptor drugs were not reversed by the opioid receptor antagonists naloxone and naltrexone. Finally, σ receptors were recognized as specific, non-opioid, non-PCP, but haloperidol-sensitive binding sites consisting of σ_1 and σ_2 subtypes. The two σ receptor subtypes can be differentiated by molecular weight, tissue distribution, and ligand binding profile.

It has been shown that the σ_1 receptor plays an important role in several socially relevant human diseases including schizophrenia, depression, Alzheimer's disease, and drug/alcohol addiction. Antagonists at the σ_1 receptor potentiate the pain-relieving effects of opioid analgesics and, moreover, can be used for the treatment of neurogenic pain. Due to their overexpression in several human tumor cell lines, σ_1 and σ_2 receptors are interesting targets for tumor therapy and diagnosis.

In the lecture the interactions of ligands with the binding site of the σ_1 receptor are analyzed. The design and synthesis of novel σ_1 receptor ligands are presented. Spirocyclic piperidines represent very promising σ_1 receptor ligands for further pharmacological evaluation. The development of a PET tracer for the imaging of σ_1 receptors in the central nervous system is shown.