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Sigma-1 receptor as a potential pharmacological target for the treatment of neuropathology

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Abstract

Sigma receptors are usually classified as a separate class of intracellular receptors. Among them the sigma-1 receptor has been the most studied regarding its pharmacological applications. This receptor with average or high affinity binds a wide range of chemical compounds of very different structural classes and a variety of therapeutic and pharmacological properties. The sigma-1 receptor is a trans-membrane protein placed in the endoplasmic reticulum (ER), which regulates the function of inositol-3-phosphate receptor, stabilizing the calcium signaling between ER and mitochondria. There are studies that the sigma-1 receptor is involved in the formation of many neurological and psychiatric conditions. It is assumed that the sigma-1 receptor acts as a sensor of normal calcium operation. The studies over the recent years have shown the role of the violation in calcium signaling in the pathogenesis of Alzheimer's and Huntington's diseases. In particular, changes in calcium homeostasis of the endoplasmic reticulum lead to the break of synaptic connections in the neurons. Thus, the sigma-1 receptor holds promise in application as a potential therapeutic target for the treatment of neuropathological diseases.

Keywords: Sigma-1 receptor; Endoplasmic reticulum; Calcium signaling; Chaperone activity; Neuropathology.

Introduction

Numerous data of preclinical studies performed on various models of memory impairment indicates that agonists of sigma-1 receptors show much promise as drugs to treat cognitive dysfunction [1,2,20,61–63]. Adjusting the excitability of the neuronal plasma membrane through the sigma-1 receptor probably plays a key role in preventing neurologic diseases.

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Generally, it can be claimed with certainty that the sigma-1 receptor acts as an intracellular modulator:

between the endoplasmic reticulum (ER) and the mitochondria,
between the ER and the cell nuclei,
between the ER and the membrane,
as well as a modulator of intracellular signaling.

Since the sigma-1 receptor binds a wide range of chemical compounds of very different structural classes with various therapeutic properties, it is of great interest for pharmacology. The researchers of the Laboratory of Molecular Neurodegeneration (LMN) of the Peter the Great St. Petersburg Polytechnic University support the calcium hypothesis of neuropathology. This hypothesis indicates that the disruption of calcium signaling plays a key role in the emergence and development of neurodegenerative diseases. The sigma-1 receptor, which is the subject of this review, regulates the function of the inositol trisphosphate receptor, thus stabilizing calcium signaling between mitochondria and the endoplasmic reticulum.

Consequently, our greatest interest in studying the sigma-1 receptor is in revealing its biophysical role in forming neurological and psychiatric conditions, as well as in regulating intracellular concentrations of calcium ions and calcium signaling.

The purpose of this review is to analyze the information in the current literature regarding the sigma-1 receptor, its structure and biophysical role in cells, and the participation of this receptor in normal and pathological processes.

Sigma receptors were originally considered a type of opioid receptors, but now they are classified as a separate class of receptors with unique structure and the set of binding ligands. Among this type of receptors, the sigma-1 receptor is the most pharmacologically studied.

The sigma-1 receptor has a protective function in different tissues. The effect of this receptor is mediated by regulation of cell metabolism, suggesting its involvement in various neuropsychiatric diseases [1]. These receptors regulate various ion channels, including potassium, calcium, chlorine, and NMDA-receptors, release various neurotransmitters, provide lipid transport and brain-derived neurotrophic factor (BDNF) signaling, myelination, neurito- and synaptogenesis, which shows high therapeutic potential for the sigma-1 receptor ligands. The modulating effect of sigma-1 receptors on neurotransmitter systems includes enhancing the glutamatergic, cholinergic, and serotoninergic neurotransmission. In contrast, the activation of sigma-1 receptors reduces the intensity of noradrenaline release and gamma-aminobutyric acid. An increase or a decrease of the calcium current due to the effect of sigma-1 receptors explains why the selective agonists of these receptors can modulate a wide range of neuronal effects, including a key mechanism by which sigma-1 receptors influence learning and memory processes [2].

Molecular biology of the sigma-1 receptor

This receptor is a highly conserved mammalian protein [3,4]. Sequence alignment showed that the protein sequence is 30% identical (the homology is 67%) to yeast C8-C7 sterol isomerase, but the receptor itself does not exhibit this enzymatic activity [5].

The gene of the sigma-1 receptor is located on chromosome 9p13, known due to its being associated with psychotic disorders [6]. The sigma-1 receptor, with its small size (223 amino-acid residue), binds with medium or high affinity to a wide range of chemical compounds of very different structural classes with various pharmacological and therapeutic properties. Among its ligands there are such compounds as benzomorphans (SKF-10047, pentazocine, dextromethorphan), antipsychotics (haloperidol), antidepressants (fluvoxamine), steroids (progesterone), antihistamines (chlorpheniramine), nuclear hormone receptor ligands (tamoxifen), Ca^{2+} channel antagonists (verapamil, emopamil), antifungals (fenpropimorph, tridemorph) and drugs of abuse (methamphetamine, cocaine, and N,N-dimethyltryptamine) [7]. However, the sigma-1 receptor knockout mice are viable as well as fertile, and do not exhibit any apparent changes in the phenotype except for a reduced hypermotor activity in response to SKF-10047 stimulation compared to wild-type mice. This fact supports the idea that the sigma-1 receptor is involved in response to psychostimulatory actions [8].

Sigma-1 receptors are widely spread in the central nervous system, liver, kidneys, and lungs, in the endocrine, immune and reproductive tissues [9]. This receptor is a transmembrane protein specifically located in ceramide- and cholesterol-rich lipid microdomains associated with the mitochondria of the ER membrane. It regulates the function of the inositol-3-phosphate receptor, stabilizing calcium signaling between the ER and the mitochondrion. It has been shown that the sigma-1 receptor forms Ca^{2+}-regulating trimeric complex with ankyrin-B and the inositol-3-phosphate receptor in NG-108 neuroblastoma cells [10].