**Chaperone Sigma1R and Antidepressant Effect**

**Subjects:** Clinical Neurology  
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## Definition

The Sigma1R chaperone interacts with cellular mechanisms, which are associated with the formation of a depressive phenotype. Sigma1R is also involved in the pharmacodynamics of antidepressants with various pharmacological targets. As a result of ligand activation, Sigma1R is capable of intracellular translocation from the endoplasmic reticulum (ER) into the region of nuclear and cellular membranes, where it interacts with resident proteins. This unique property of Sigma1R provides regulation of various receptors, ion channels, enzymes, and transcriptional factors. Pharmacological activation of chaperone Sigma1R can be considered a promising strategy to improve and develop approaches for combined, adjuvant pharmacotherapy of depression.

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## 1. Introduction

The incidence of depressive disorders is growing steadily and represents an acute medical and social problem\(^1\). Antidepressants used in clinical practice have proved their efficacy in long-term treatment\(^2\). However, such medication is accompanied by various side effects\(^3\), and about one-third of patients do not achieve remission\(^4\). The development of new treatment options for depressive disorders becomes possible due to numerous studies of their pathogenesis. The monoamine hypothesis of depression was among the first proposed and was based on the efficiency of drugs that increase the levels of 5-HT or a combination of catecholamines in the synaptic cleft\(^5\). Recent studies suggest that a convergence of different molecular mechanisms may be associated with depressive disorders\(^7\). There is a growing body of evidence supporting the neurotrophin theory of depression, according to which the major role that impaired BDNF/trkB signaling in the hippocampus and prefrontal cortex plays in depression\(^8\). The contribution of inflammation, activation of microglia, and lipid peroxidation (LPO) processes on the pathogenesis of depression have also been revealed\(^9\). The role of glutamatergic processes in the development of depressive disorders and rapid antidepressant action has been confirmed experimentally\(^10\). The importance of potassium channels, intracellular calcium, and post-receptor signaling pathways has been demonstrated\(^11\). In the 1990s, sigma-1 receptors (Sigma1R) were considered as a pharmacological target for antidepressants. A prerequisite for these studies was the discovery of the affinity of antidepressants from the group of 5-HT reuptake inhibitors (SSRIs) for Sigma1R\(^12\). The antidepressant effect of most SSRIs is associated with a high affinity for the sodium-dependent serotonin transporter (SERT); however, no similar association with the affinity for Sigma1R was demonstrated\(^13\). At the same time, the ability of selective antagonists of Sigma1R to block the rapid and delayed antidepressant-like action of fluvoxamine, venlafaxine, and endogenous and exogenous agonists of Sigma1R, after a single administration, has been shown\(^14\). An attempt to introduce selective Sigma1R agonists into clinical practice as antidepressant drugs was unsuccessful\(^15\). Despite these findings, discoveries in molecular biology have revealed three important properties of Sigma1R: chaperone activity aimed at a large number of proteins, intracellular translocation within lipid microdomains, and interaction with a large number of chemical compounds\(^16\).

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## 2. Structure and Functional Activity of the Chaperone Sigma1R

Sigma1R was first identified in the Tsung Ping Su laboratory in 1982\(^17\). To date, the Sigma1R chaperone activity has been established, and a significant body of scientific data on the structure, functional activity, and ligand regulation of Sigma1R has been collected. Most of the studies are systematized and presented in detailed reviews\(^18\). The human, murine, rat, and guinea pig Sigma1R protein comprises 223 amino acid residues (\(-25\) kDa) that are more than 90\% identical. Sigma1R has a unique amino acid sequence and has no homology with known mammalian proteins\(^19\). In 2016 the crystal structure of a protein with one transmembrane domain for each monomer was determined under the general supervision of Andrew C. Kruse\(^20\). Sigma1R oligomerization affects the chaperone functional activity and depends on the interaction with ligands\(^21\).
Chaperone Sigma1R is expressed in certain regions of the rodent brain, including the cortex and hippocampus. The data obtained in laboratory animals are consistent with the distribution of Sigma1R in the human brain. Sigma1R is a resident protein of the endoplasmic reticulum (ER) and is predominantly localized in the cholesterol-rich region of ER mitochondria-associated membranes (MAM). In this compartment, Sigma1R acts as a chaperone to stabilize IP3R3, maintaining Ca2+ flow from the ER to mitochondria and ATP production. Chaperone Sigma1R acts ligand-dependently on ER Ca2+ sensor STIM1 and regulates store-operated Ca2+ entry. The chaperone interaction with the VDAC2 channel influences the uptake of cholesterol and the synthesis of pregnenolone in mitochondria. Sigma1R stabilizes the ER stress sensor IRE1, thereby prolonging its dimerization and promoting endonuclease activity and the production of a functionally active transcription factor, XBP1, which induces the expression of genes for neurotrophins, antioxidant defense proteins, and chaperones. Sigma1R is able to form a Ca2+ sensitive complex with the main ER chaperone BiP (GRP 78, HSPA5), which dissociates under the action of Sigma1R agonists, activating BiP. The interaction of BiP and ER stress sensors IRE1, PERK, and ATF6 inhibits their activity. In turn, without the ER stress and in combination with IRE1, BiP itself acts as an ER stress sensor and does not perform its normal chaperone functions. The activity of Sigma1R in the MAM region is significant for the response to ER stress (UPR, unfolded protein response) in pathological conditions. The interaction of Sigma1R with Rac1-GTPase influences the redox processes in neurons and the formation of dendritic spines. The involvement of the chaperone in the regulation of p35 protein metabolism (CDK5 activator 1) is of paramount importance in axon elongation.

Sigma1R is involved in the formation of ER lipid compartments. During ligand activation or under conditions of cellular stress, the chaperone, as part of lipid microdomains, is capable of both redistribution within the ER and translocation into the region of the plasma and nuclear membranes. Sigma1R engages in protein–protein interactions and regulates the functional activity of G-protein coupled receptors (dopamine D1 and D2, opioid µ, cannabinoid CB1), tyrosine kinase receptor for neurotrophins trkB, receptor for platelet growth factor PDGFRB, ion channels (ASICs, Kv1.2, Kv1.3, Kv2.1, Nav1.2, and GluN1), and other plasma membrane proteins. The interaction of Sigma1R with emerin on the nucleus inner membrane provides the formation of the chromatin remodeling protein complex, its interaction with the Sp3 protein, and regulation of the transcription of target genes. The client proteins of the Sigma1R chaperone are involved in the pathogenesis of depressive disorders, which indicates the importance of Sigma1R for the pharmacodynamics of antidepressants. The effects of Sigma1R on proteins are not limited to experimentally confirmed chaperone interactions. For example, upon ligand activation, Sigma1R enhances the expression of subunits (GluN2A, GluN2B) and the traffic of NMDA receptors to the plasma membrane of neurons and regulates the activity of various types of Ca2+ channels. Recent studies have uncovered the importance of Sigma1R in the modulation of mir-214-3p, the level of which is increased in Sigmar1−/− cells of the retina of rd10 mice and the prefrontal cortex of mice after chronic social defeat stress. Selective agonist of Sigma1R (+)-pentazocine (0.5 mg/kg, i.p.), which has an antidepressant-like effect, decreased the level of mir-214-3p in retinal cells. The contribution of the mir-214-3p in the nucleus accumbens (NAc) to both the pathogenesis of depression and the pharmacodynamics of escitalopram was revealed in chronic unpredictable mild stress model in rats.

Thus, upon ligand activation, chaperone Sigma1R is capable of translocation between intracellular compartments and interactions with client proteins expressed in the brain and involved in the pathogenesis of depressive disorders and the pharmacodynamics of antidepressants. The latest studies also demonstrate the role of Sigma1R in epigenetic processes that promote antidepressant action. Therefore, pharmacological activation of chaperone Sigma1R can be considered a promising strategy to improve and develop approaches for combined, adjuvant pharmacotherapy of depression.

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