Chaperone Sigma1R and Antidepressant Effect

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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.

Keywords: Sigma1R chaperone ; depression ; antidepressants

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][6]. 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][9]. The contribution of inflammation, activation of microglia, and lipid peroxidation (LPO) processes on the pathogenesis of depression have also been revealed [10][11][12][13][14]. The role of glutamatergic processes in the development of depressive disorders and rapid antidepressant action has been confirmed experimentally [15][16][17]. The importance of potassium channels, intracellular calcium, and post-receptor signaling pathways has been demonstrated [18][19][20]. 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 [21]. 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 [21][22][23][24][25]. 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 [26][27][28][29][30][31]. An attempt to introduce selective Sigma1R agonists into clinical practice as antidepressant drugs was unsuccessful [32][33][34]. 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 [35][36][37].

2. Structure and Functional Activity of the Chaperone Sigma1R

Sigma1R was first identified in the Tsung Ping Su laboratory in 1982 [38]. 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 [35][36][39][40][41][42][43][44]. 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 [43][44]. 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 [45][46]. Sigma1R oligomerization affects the chaperone functional activity and depends on the interaction with ligands [41][47][48][49][50].

Chaperone Sigma1R is expressed in certain regions of the rodent brain, including the cortex and hippocampus [51][52][53][54][55]. The data obtained in laboratory animals are consistent with the distribution of Sigma1R in the human brain [56]. 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) [35][40][57][58]. In this compartment, Sigma1R acts as a chaperone to stabilize IP_3R3, maintaining Ca^{2+} flow from the ER to mitochondria and ATP production [59]. Chaperone Sigma1R acts ligand-dependently on ER Ca^{2+} sensor STIM1 and regulates store-operated Ca^{2+} entry [60]. The chaperone interaction with the VDAC2 channel influences the uptake of cholesterol and the synthesis of pregnenolone in mitochondria [61][62]. 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 [63][64]. Sigma1R is able to form a Ca^{2+} sensitive complex with the main ER chaperone BiP (GRP 78, HSPA5) [59][65], which dissociates under the action of Sigma1R agonists, activating BiP [59][66]. The interaction of BiP and ER stress sensors IRE1, PERK, and ATF6 inhibits their activity [67]. 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 [68]. The activity of Sigma1R in the MAM region is significant for the response to ER stress (UPR, unfolded protein response) in pathological conditions [40][69]. The interaction of Sigma1R with Rac1-GTPase influences the redox processes in neurons and the formation of dendritic spines [70][71]. The involvement of the chaperone in the regulation of p35 protein metabolism (CDK5 activator 1) is of paramount importance in axon elongation [72].

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 [66][73][74]. Sigma1R engages in protein–protein interactions and regulates the functional activity of G-protein coupled receptors (dopamine D_1 and D_2, opioid μ, cannabinoid CB_1), tyrosine kinase receptor for neurotrophins trkB, receptor for platelet growth factor PDGFRβ, ion channels (ASICs, $K_V1.2$, $K_V1.3$, $K_V2.1$, $Na_V1.2$, and GluN1), and other plasma membrane proteins [35][39][41]. 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 [35][75]. The client proteins of the Sigma1R chaperone are involved in the pathogenesis of depressive disorders [76][77][78][79][80][81][82][83], 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 [84] and regulates the activity of various types of Ca^{2+} channels [85][86]. 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 [87] and the prefrontal cortex of mice after chronic social defeat stress [88]. Selective agonist of Sigma1R (+)-pentazocine (0.5 mg/kg, i.p.), which has an antidepressant-like effect [30][89], decreased the level of mir-214-3p in retinal cells [87]. 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 [90].

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.

References

1. Qingqing Liu; Hairong He; Jin Yang; Xiaojie Feng; Fanfan Zhao; Jun Lyu; Changes in the global burden of depression fr om 1990 to 2017: Findings from the Global Burden of Disease study. *Journal of Psychiatric Research* **2020**, *126*, 134-1 40, 10.1016/j.jpsychires.2019.08.002.
2. Andrea Cipriani; Toshi A Furukawa; Georgia Salanti; Anna Chaimani; Lauren Z Atkinson; Yusuke Ogawa; Stefan Leuch t; Henricus G Ruhe; Erick H Turner; Julian P T Higgins; et al. Comparative efficacy and acceptability of 21 antidepressa nt drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analys is. *The Lancet* **2018**, *391*, 1357-1366, 10.1016/s0140-6736(17)32802-7.
3. Janus Christian Jakobsen; Christian Gluud; Irving Kirsch; Should antidepressants be used for major depressive disorde r?. *BMJ Evidence-Based Medicine* **2019**, *25*, 130-130, 10.1136/bmjebm-2019-111238.

4. A. John Rush; Madhukar H. Trivedi; Stephen R. Wisniewski; Andrew A. Nierenberg; Jonathan W. Stewart; Diane Warde n; George Niederehe; Michael Thase; Philip W. Lavori; Barry D. Lebowitz; et al. Acute and Longer-Term Outcomes in D epressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. *American Journal of Psychiatry* **2 006**, *163*, 1905-1917, 10.1176/ajp.2006.163.11.1905.

5. Philip J Cowen; Neuroendocrine and Neurochemical Processes in Depression. *Psychopathology Review* **2016**, *a3*, 3-1 5, 10.5127/pr.034513.

6. Fiammetta Cosci; Guy Chouinard; The Monoamine Hypothesis of Depression Revisited: Could It Mechanistically Novel Antidepressant Strategies?. *Neurobiology of Depression* **2019**, *n/a*, 63-73, 10.1016/b978-0-12-813333-0.00007-x.

7. Bangshan Liu; Jin Liu; Mi Wang; Yan Zhang; Lingjiang Li; From Serotonin to Neuroplasticity: Evolvement of Theories fo r Major Depressive Disorder. *Frontiers in Cellular Neuroscience* **2017**, *11*, 305, 10.3389/fncel.2017.00305.

8. Ronald S. Duman; Satoshi Deyama; Manoela Viar Fogaça; Role of BDNF in the pathophysiology and treatment of depr ession: Activity-dependent effects distinguish rapid-acting antidepressants. *European Journal of Neuroscience* **2019**, *n/ a*, n/a, 10.1111/ejn.14630.

9. Minal Jaggar; Sashaina E. Fanibunda; Shreya Ghosh; Ronald S. Duman; Vidita A. Vaidya; The Neurotrophic Hypothesi s of Depression Revisited: New Insights and Therapeutic Implications. *Neurobiology of Depression* **2019**, *n/a*, 43-62, 1 0.1016/b978-0-12-813333-0.00006-8.

10. Yash B. Joshi; Domenico Praticò; Lipid Peroxidation in Psychiatric Illness: Overview of Clinical Evidence. *Oxidative Me dicine and Cellular Longevity* **2014**, *2014*, 1-5, 10.1155/2014/828702.

11. Magdalena Sowa-Kućma; Krzysztof Styczeń; Marcin Siwek; Paulina Misztak; Rafał J. Nowak; Dominika Dudek; Janusz K. Rybakowski; Gabriel Nowak; Michael Maes; Lipid Peroxidation and Immune Biomarkers Are Associated with Major Depression and Its Phenotypes, Including Treatment-Resistant Depression and Melancholia. *Neurotoxicity Research* **2 017**, *33*, 448-460, 10.1007/s12640-017-9835-5.

12. Lijuan Zhang; Jinqiang Zhang; Zili You; Switching of the Microglial Activation Phenotype Is a Possible Treatment for De pression Disorder. *Frontiers in Cellular Neuroscience* **2018**, *12*, 306, 10.3389/fncel.2018.00306.

13. Jennifer C. Felger; Role of Inflammation in Depression and Treatment Implications. *Calcitonin Gene-Related Peptide (CGRP) Mechanisms* **2018**, *250*, 255-286, 10.1007/164_2018_166.

14. Chieh-Hsin Lee; Fabrizio Giuliani; The Role of Inflammation in Depression and Fatigue. *Frontiers in Immunology* **2019**, *10*, 1696, 10.3389/fimmu.2019.01696.

15. Eileen O'toole; Marika V. Doucet; Eoin Sherwin; Andrew Harkin; Novel Targets in the Glutamate and Nitric Oxide Neuro transmitter Systems for the Treatment of Depression. *Systems Neuroscience in Depression* **2016**, *n/a*, 81-113, 10.101 6/b978-0-12-802456-0.00003-0.

16. Jeffrey M. Witkin; Anna E. Martin; Lalit K. Golani; Nina Z. Xu; Jodi L. Smith; Rapid-acting antidepressants. *Studies in S urface Science and Catalysis* **2019**, *86*, 47-96, 10.1016/bs.apha.2019.03.002.

17. Chun Yang; Jianjun Yang; Ailin Luo; K. Hashimoto; Molecular and cellular mechanisms underlying the antidepressant ef fects of ketamine enantiomers and its metabolites. *Translational Psychiatry* **2019**, *9*, 280-11, 10.1038/s41398-019-0624 -1.

18. Allyson K. Friedman; Barbara Juarez; Stacy M. Ku; Hongxing Zhang; Rhodora C. Calizo; J.J. Walsh; Dipesh Chaudhur y; Song Zhang; Angel Hawkins; David M. Dietz; et al. KCNQ channel openers reverse depressive symptoms via an acti ve resilience mechanism. *Nature Communications* **2016**, *7*, 11671, 10.1038/ncomms11671.

19. Paul J. Harrison; Nicola Hall; Arne Mould; Noura Al-Juffali; Elizabeth M. Tunbridge; Cellular calcium in bipolar disorder: systematic review and meta-analysis. *Molecular Psychiatry* **2019**, *n/a*, 1-11, 10.1038/s41380-019-0622-y.

20. Gislaine Z. Réus; Jaqueline S. Generoso; Ana Lúcia S. Rodrigues; João Quevedo; Intracellular Signaling Pathways Im plicated in the Pathophysiology of Depression. *Neurobiology of Depression* **2019**, *n/a*, 97-109, 10.1016/b978-0-12-813 333-0.00010-x.

21. Natsuko Narita; Kenji Hashimoto; Shin-ichiro Tomitaka; Yoshio Minabe; Interactions of selective serotonin reuptake inhi bitors with subtypes of sigma receptors in rat brain. *European Journal of Pharmacology* **1996**, *307*, 117-119, .

22. Masahiko Tatsumi; Karen Groshan; Randy D Blakely; Elliott Richelson; Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *European Journal of Pharmacology* **1997**, *340*, 249-258, 10.10 16/s0014-2999(97)01393-9.

23. Tamaki Ishima; Yuko Fujita; K. Hashimoto; Interaction of new antidepressants with sigma-1 receptor chaperones and th eir potentiation of neurite outgrowth in PC12 cells. *European Journal of Pharmacology* **2014**, *727*, 167-173, 10.1016/j.ej phar.2014.01.064.

24. Ewgeni Jakubovski; Anjali L. Varigonda; Nicholas Freemantle; Matthew Taylor; Michael H. Bloch; Systematic Review a nd Meta-Analysis: Dose-Response Relationship of Selective Serotonin Reuptake Inhibitors in Major Depressive Disord er. *American Journal of Psychiatry* **2015**, *173*, 174-83, 10.1176/appi.ajp.2015.15030331.

25. Kohji Fukunaga; Shigeki Moriguchi; Stimulation of the Sigma-1 Receptor and the Effects on Neurogenesis and Depress ive Behaviors in Mice. *Retinal Degenerative Diseases* **2017**, *964*, 201-211, 10.1007/978-3-319-50174-1_14.

26. Yumi Sugimoto; Noriko Tagawa; Yoshiharu Kobayashi; Kumiko Mitsui-Saito; Yoshihiro Hotta; Jun Yamada; Involvement of the sigma1 receptor in the antidepressant-like effects of fluvoxamine in the forced swimming test in comparison with the effects elicited by paroxetine. *European Journal of Pharmacology* **2012**, *696*, 96-100, 10.1016/j.ejphar.2012.09.030.

27. Ashish Dhir; S. K. Kulkarni; Involvement of sigma-1 receptor modulation in the antidepressant action of venlafaxine. *Ne uroscience Letters* **2007**, *420*, 204-208, 10.1016/j.neulet.2007.04.055.

28. Ashish Dhir; Sk Kulkarni; Involvement of sigma (σ1) receptors in modulating the anti-depressant effect of neurosteroids (dehydroepiandrosterone or pregnenolone) in mouse tail-suspension test. *Journal of Psychopharmacology* **2008**, *22*, 6 91-696, 10.1177/0269881107082771.

29. Grażyna Skuza; Zofia Rogóż; Antidepressant-like effect of PRE-084, a selective σ1 receptor agonist, in Albino Swiss an d C57BL/6J mice. *Pharmacological Reports* **2009**, *61*, 1179-1183, 10.1016/s1734-1140(09)70181-1.

30. M Ukai; H Maeda; Y Nanya; T Kameyama; K Matsuno; Beneficial effects of acute and repeated administrations of sigm a receptor agonists on behavioral despair in mice exposed to tail suspension.. *Pharmacology Biochemistry and Behavi or* **1998**, *61*, 247-52, .

31. Lilla Lenart; Judit Hodrea; Adam Hosszu; Sandor Koszegi; Dora Zelena; Dora Balogh; Edgar Szkibinszkij; Apor Veres-S zékely; Laszlo Wagner; Ádám Vannay; et al. The role of sigma-1 receptor and brain-derived neurotrophic factor in the d evelopment of diabetes and comorbid depression in streptozotocin-induced diabetic rats. *Psychopharmacology* **2016**, *2 33*, 1269-1278, 10.1007/s00213-016-4209-x.

32. H P Volz; K. Stoll; Clinical Trials with Sigma Ligands. *Pharmacopsychiatry* **2004**, *37*, 214-220, 10.1055/s-2004-832680.

33. Jordanna E. Bermack; Guy Debonnel; The Role of Sigma Receptors in Depression. *Journal of Pharmacological Scienc es* **2005**, *97*, 317-336, 10.1254/jphs.crj04005x.

34. Teruo Hayashi; Shang-Yi Tsai; Tomohisa Mori; Michiko Fujimoto; Tsung-Ping Su; Hayashi Teruo; Tsai Shang-Yi; Mori To mohisa; Fujimoto Michiko; Su Tsung-Ping; et al. Targeting ligand-operated chaperone sigma-1 receptors in the treatme nt of neuropsychiatric disorders. *Expert Opinion on Therapeutic Targets* **2011**, *15*, 557-77, 10.1517/14728222.2011.56 0837.

35. Tsung-Ping Su; Tzu-Chieh Su; Yoki Nakamura; Shang-Yi Tsai; The Sigma-1 Receptor as a Pluripotent Modulator in Livi ng Systems.. *Trends in Pharmacological Sciences* **2016**, *37*, 262-278, 10.1016/j.tips.2016.01.003.

36. Daniel A. Ryskamp; Svetlana Korban; Vladimir Zhemkov; Nina Kraskovskaya; Ilya B. Bezprozvanny; Neuronal Sigma-1 Receptors: Signaling Functions and Protective Roles in Neurodegenerative Diseases. *Frontiers in Neuroscience* **2019**, *13*, 862, 10.3389/fnins.2019.00862.

37. Felix J. Kim; Christina M. Maher; Sigma1 Pharmacology in the Context of Cancer. *cGMP: Generators, Effectors and Th erapeutic Implications* **2017**, *244*, 237-308, 10.1007/164_2017_38.

38. T P Su; Evidence for sigma opioid receptor: binding of [3H]SKF-10047 to etorphine-inaccessible sites in guinea-pig brai n. *Journal of Pharmacology and Experimental Therapeutics* **1982**, *223*, 284-90, .

39. Colin G. Rousseaux; Stephanie F. Greene; Sigma receptors [σRs]: biology in normal and diseased states. *Journal of R eceptors and Signal Transduction* **2015**, *36*, 1-62, 10.3109/10799893.2015.1015737.

40. Benjamin Delprat; Lucie Crouzier; Tsung-Ping Su; Tangui Maurice; At the Crossing of ER Stress and MAMs: A Key Rol e of Sigma-1 Receptor?. *Retinal Degenerative Diseases* **2020**, *1131*, 699-718, 10.1007/978-3-030-12457-1_28.

41. Uyen B. Chu; Arnold E. Ruoho; Biochemical Pharmacology of the Sigma-1 Receptor. *Molecular Pharmacology* **2015**, *8 9*, 142-153, 10.1124/mol.115.101170.

42. Frauke Weber; Bernhard Wünsch; Medicinal Chemistry of σ1 Receptor Ligands: Pharmacophore Models, Synthesis, St ructure Affinity Relationships, and Pharmacological Applications. *cGMP: Generators, Effectors and Therapeutic Implicat ions* **2017**, *244*, 51-79, 10.1007/164_2017_33.

43. Felipe Ossa; Jason R. Schnell; Jose Luis L. Ortega-Roldan; A Review of the Human Sigma-1 Receptor Structure. *Adva nces in Experimental Medicine and Biology* **2017**, *964*, 15-29, 10.1007/978-3-319-50174-1_3.

44. Andrew C. Kruse; Structural Insights into Sigma1 Function. *cGMP: Generators, Effectors and Therapeutic Implications* **2016**, *244*, 13-25, 10.1007/164_2016_95.

45. Hayden R. Schmidt; Sanduo Zheng; Esin Gurpinar; Antoine Koehl; Aashish Manglik; Andrew C. Kruse; Crystal structure of the human σ1 receptor. *Nature* **2016**, *532*, 527-530, 10.1038/nature17391.

46. Assaf Alon; Hayden R. Schmidt; Sanduo Zheng; Andrew C. Kruse; Structural Perspectives on Sigma-1 Receptor Function. *Advances in Experimental Medicine and Biology* **2017**, *964*, 5-13, 10.1007/978-3-319-50174-1_2.

47. Ara M. Abramyan; Hideaki Yano; Min Xu; Leanne Liu; Sett Naing; Andrew D. Fant; Lei Shi; The Glu102 mutation disrupts higher-order oligomerization of the sigma 1 receptor. *Computational and Structural Biotechnology Journal* **2020**, *18*, 199-206, 10.1016/j.csbj.2019.12.012.

48. Hideaki Yano; Leanne Liu; Sett Naing; Lei Shi; The Effects of Terminal Tagging on Homomeric Interactions of the Sigma 1 Receptor. *Frontiers in Neuroscience* **2019**, *13*, 1356, 10.3389/fnins.2019.01356.

49. Ashish K. Mishra; Timur Mavlyutov; D. R. Singh; Gabriel Biener; Jay Yang; Julie A. Oliver; Arnold E. Ruoho; Valerica Raicu; The sigma-1 receptors are present in monomeric and oligomeric forms in living cells in the presence and absence of ligands. *Biochemical Journal* **2015**, *466*, 263-271, 10.1042/bj20141321.

50. Katarzyna A. Gromek; Fabian P. Suchy; Hannah R. Meddaugh; Russell L. Wrobel; Loren M. Lapointe; Uyen B. Chu; John G. Primm; Arnold E. Ruoho; Alessandro Senes; Brian G. Fox; et al. The Oligomeric States of the Purified Sigma-1 Receptor Are Stabilized by Ligands. *Journal of Biological Chemistry* **2014**, *289*, 20333-20344, 10.1074/jbc.m113.537993.

51. G Alonso; V.-L Phan; I Guillemain; M Saunier; A Legrand; M Anoal; Tangui Maurice; Immunocytochemical localization of the sigma1 receptor in the adult rat central nervous system. *Neuroscience* **2000**, *97*, 155-170, 10.1016/s0306-4522(00)00014-2.

52. Xavier Guitart; Xavier Codony; Xavier Monroy; Sigma receptors: biology and therapeutic potential. *Psychopharmacology* **2004**, *174*, 301-319, 10.1007/s00213-004-1920-9.

53. Michelle L. James; Bin Shen; Cristina L. Zavaleta; Carsten H. Nielsen; Christophe Mesangeau; Pradeep K. Vuppala; Carmel Chan; Bonnie A. Avery; James A. Fishback; Rae R. Matsumoto; et al. New Positron Emission Tomography (PET) Radioligand for Imaging σ-1 Receptors in Living Subjects. *Journal of Medicinal Chemistry* **2012**, *55*, 8272-8282, 10.1021/jm300371c.

54. Shenuarin Bhuiyan; Hideaki Tagashira; Kohji Fukunaga; Crucial interactions between selective serotonin uptake inhibitors and sigma-1 receptor in heart failure. *Journal of Pharmacological Sciences* **2013**, *121*, 177-184, 10.1254/jphs.12r13cp.

55. Yu Lan; Ping Bai; Zude Chen; Ramesh Neelamegam; Michael S. Placzek; Hao Wang; Stephanie A. Fiedler; Jing Yang; Gengyang Yuan; Xiying Qu; et al. Novel radioligands for imaging sigma-1 receptor in brain using positron emission tomography (PET). *Acta Pharmaceutica Sinica B* **2019**, *9*, 1204-1215, 10.1016/j.apsb.2019.07.002.

56. Jun Toyohara; Muneyuki Sakata; Kiichi Ishiwata; Imaging of sigma1 receptors in the human brain using PET and [11C]SA4503. *Central Nervous System Agents in Medicinal Chemistry* **2009**, *9*, 190-196, 10.2174/1871524910909030190.

57. Teruo Hayashi; Tsung-Ping Su; Cholesterol at the Endoplasmic Reticulum: Roles of the Sigma-1 Receptor Chaperone and Implications thereof in Human Diseases. *Subcellular Biochemistry* **2010**, *51*, 381-398, 10.1007/978-90-481-8622-8_13.

58. Zhangsen Zhou; Mauricio Torres; Haibo Sha; Christopher J. Halbrook; Françoise Van Den Bergh; Rachel B. Reinert; Tatsuya Yamada; Siwen Wang; Yingying Luo; Allen H. Hunter; et al. Endoplasmic reticulum–associated degradation regulates mitochondrial dynamics in brown adipocytes. *Science* **2020**, *368*, 54-60, 10.1126/science.aay2494.

59. Teruo Hayashi; Tsung-Ping Su; Sigma-1 Receptor Chaperones at the ER- Mitochondrion Interface Regulate Ca2+ Signaling and Cell Survival. *Cell* **2007**, *131*, 596-610, 10.1016/j.cell.2007.08.036.

60. Shyam Srivats; Dilshan Balasuriya; Mathias Pasche; Gerard Vistal; J. Michael Edwardson; Colin W. Taylor; Ruth D. Murrell-Lagnado; Sigma1 receptors inhibit store-operated Ca2+ entry by attenuating coupling of STIM1 to Orai1. *The Journal of Cell Biology* **2016**, *213*, 65-79, 10.1083/jcb.201506022.

61. Karla-Sue C. Marriott; Manoj Prasad; Veena Thapliyal; Himangshu S. Bose; σ-1 Receptor at the Mitochondrial-Associated Endoplasmic Reticulum Membrane Is Responsible for Mitochondrial Metabolic Regulation. *Journal of Pharmacology and Experimental Therapeutics* **2012**, *343*, 578-586, 10.1124/jpet.112.198168.

62. Manoj Prasad; Jasmeet Kaur; Kevin J. Pawlak; Mahuya Bose; Randy M. Whittal; Himangshu S. Bose; Mitochondria-associated Endoplasmic Reticulum Membrane (MAM) Regulates Steroidogenic Activity via Steroidogenic Acute Regulatory Protein (StAR)-Voltage-dependent Anion Channel 2 (VDAC2) Interaction*. *Journal of Biological Chemistry* **2014**, *290*, 2604-2616, 10.1074/jbc.M114.605808.

63. Tomohisa Mori; Teruo Hayashi; Eri Hayashi; Tsung-Ping Su; Sigma-1 Receptor Chaperone at the ER-Mitochondrion Interface Mediates the Mitochondrion-ER-Nucleus Signaling for Cellular Survival. *PLoS ONE* **2013**, *8*, e76941, 10.1371/journal.pone.0076941.

64. Atsushi Saito; Longjie Cai; Koji Matsuhisa; Yosuke Ohtake; Masayuki Kaneko; Soshi Kanemoto; Rie Asada; Kazunori I maizumi; Neuronal activity-dependent local activation of dendritic unfolded protein response promotes expression of br ain-derived neurotrophic factor in cell soma. *Journal of Neurochemistry* **2017**, *144*, 35-49, 10.1111/jnc.14221.

65. Jose Luis L. Ortega-Roldan; Felipe Ossa; Jason R. Schnell; Characterization of the Human Sigma-1 Receptor Chapero ne Domain Structure and Binding Immunoglobulin Protein (BiP) Interactions. *Journal of Biological Chemistry* **2013**, *28 8*, 21448-21457, 10.1074/jbc.m113.450379.

66. Teruo Hayashi; Tsung-Ping Su; Intracellular Dynamics of σ-1 Receptors (σ1 Binding Sites) in NG108-15 Cells. *Journal of Pharmacology and Experimental Therapeutics* **2003**, *306*, 726-733, 10.1124/jpet.103.051292.

67. Elif Karagöz; Diego Acosta-Alvear; Peter Walter; The Unfolded Protein Response: Detecting and Responding to Fluctu ations in the Protein-Folding Capacity of the Endoplasmic Reticulum. *Cold Spring Harbor Perspectives in Biology* **2019**, *11*, a033886, 10.1101/cshperspect.a033886.

68. Megan C. Kopp; Natacha Larburu; Vinoth Durairaj; Christopher J. Adams; Maruf M. U. Ali; UPR proteins IRE1 and PER K switch BiP from chaperone to ER stress sensor. *Nature Structural & Molecular Biology* **2019**, *26*, 1053-1062, 10.103 8/s41594-019-0324-9.

69. Ryuta Morihara; Toru Yamashita; Xia Liu; Koji Abe; Yusuke Fukui; Kota Sato; Yasuyuki Ohta; Nozomi Hishikawa; Jingw ei Shang; Koji Abe; et al. Protective effect of a novel sigma-1 receptor agonist is associated with reduced endoplasmic r eticulum stress in stroke male mice. *Journal of Neuroscience Research* **2018**, *96*, 1707-1716, 10.1002/jnr.24270.

70. N. Natsvlishvili; Nino Goguadze; Elene Zhuravliova; D. G. Mikeladze; Sigma-1 receptor directly interacts with Rac1-GT Pase in the brain mitochondria. *BMC Biochemistry* **2015**, *16*, 1-7, 10.1186/s12858-015-0040-y.

71. Shang-Yi Tsai; Teruo Hayashi; Brandon K. Harvey; Yun Wang; Wells W. Wu; Rong-Fong Shen; Yongqing Zhang; Kevin G. Becker; Barry J. Hoffer; Tsung-Ping Su; et al. Sigma-1 receptors regulate hippocampal dendritic spine formation via a free radical-sensitive mechanism involving Rac1·GTP pathway. *Proceedings of the National Academy of Sciences* **20 09**, *106*, 22468-22473, 10.1073/pnas.0909089106.

72. Shang-Yi A. Tsai; Michael J. Pokrass; Neal R. Klauer; Hiroshi Nohara; Tsung-Ping Su; Sigma-1 receptor regulates Tau phosphorylation and axon extension by shaping p35 turnover via myristic acid. *Proceedings of the National Academy of Sciences* **2015**, *112*, 6742-6747, 10.1073/pnas.1422001112.

73. Teruo Hayashi; Tsung-Ping Su; σ-1 Receptors (σ1 Binding Sites) Form Raft-Like Microdomains and Target Lipid Drople ts on the Endoplasmic Reticulum: Roles in Endoplasmic Reticulum Lipid Compartmentalization and Export. *Journal of Pharmacology and Experimental Therapeutics* **2003**, *306*, 718-725, 10.1124/jpet.103.051284.

74. Teruo Hayashi; Michiko Fujimoto; Detergent-resistant microdomains determine the localization of sigma-1 receptors to t he endoplasmic reticulum-mitochondria junction. *Molecular Pharmacology* **2010**, *77*, 517-28, 10.1124/mol.109.062539.

75. Shang-Yi A. Tsai; Jian-Ying Chuang; Meng-Shan Tsai; Xiao-Fei Wang; Zheng-Xiong Xi; Jan-Jong Hung; Wen-Chang C hang; Antonello Bonci; Tsung-Ping Su; Sigma-1 receptor mediates cocaine-induced transcriptional regulation by recruiti ng chromatin-remodeling factors at the nuclear envelope. *Proceedings of the National Academy of Sciences* **2015**, *112*, E6562-70, 10.1073/pnas.1518894112.

76. Wenjie Zhou; Shandong Ye; Rong Luo; Li-Min Wu; Wei Wang; Inhibition of acid-sensing ion channels reduces the hypo thalamus–pituitary–adrenal axis activity and ameliorates depression-like behavior in rats. *RSC Adv.* **2019**, *9*, 8707-871 3, 10.1039/c9ra00020h.

77. Maurice Y.F. Shen; Melissa L. Perreault; Francis R. Bambico; Jace Jones-Tabah; Marco Cheung; Theresa Fan; José N. Nobrega; Susan R. George; Rapid anti-depressant and anxiolytic actions following dopamine D1–D2 receptor heterom er inactivation. *European Neuropsychopharmacology* **2015**, *25*, 2437-2448, 10.1016/j.euroneuro.2015.09.004.

78. Ahmed Hasbi; Tuan Nguyen; Haneen Rahal; Joshua D. Manduca; Sharon Miksys; Rachel F. Tyndale; Bertha K. Madra s; Melissa L. Perreault; Susan R. George; Sex difference in dopamine D1-D2 receptor complex expression and signalin g affects depression- and anxiety-like behaviors. *Biology of Sex Differences* **2020**, *11*, 1-17, 10.1186/s13293-020-0028 5-9.

79. Chunlin Chen; Ling Wang; Xianfang Rong; Weiping Wang; Xiaoliang Wang; Effects of fluoxetine on protein expression of potassium ion channels in the brain of chronic mild stress rats. *Acta Pharmaceutica Sinica B* **2015**, *5*, 55-61, 10.101 6/j.apsb.2014.12.004.

80. Corey B. Puryear; Julie Brooks; Laura Tan; Karen Smith; Yan Li; Jacobi Cunningham; Mark S. Todtenkopf; Reginald L. Dean; Connie Sanchez; Opioid receptor modulation of neural circuits in depression: What can be learned from preclinic al data?. *Neuroscience & Biobehavioral Reviews* **2020**, *108*, 658-678, 10.1016/j.neubiorev.2019.12.007.

81. Mario Stampanoni Bassi; Luana Gilio; Pierpaolo Maffei; Ettore Dolcetti; Antonio Bruno; Fabio Buttari; Diego Centonze; Ennio Iezzi; Exploiting the Multifaceted Effects of Cannabinoids on Mood to Boost Their Therapeutic Use Against Anxie ty and Depression. *Frontiers in Molecular Neuroscience* **2018**, *11*, 424, 10.3389/fnmol.2018.00424.

82. Katharina Domschke; U. Dannlowski; Patricia Ohrmann; Bruce R. Lawford; Jochen Bauer; Harald Kugel; Walter Heindel; Ross McDonald Young; Phillip Morris; Volker Arolt; et al. Cannabinoid receptor 1 (CNR1) gene: Impact on antidepressant treatment response and emotion processing in Major Depression. *European Neuropsychopharmacology* **2008**, *18*, 751-759, 10.1016/j.euroneuro.2008.05.003.
83. Manish Kumar Jha; Abu Minhajuddin; Bharathi S Gadad; Madhukar H. Trivedi; Platelet-Derived Growth Factor as an Antidepressant Treatment Selection Biomarker: Higher Levels Selectively Predict Better Outcomes with Bupropion-SSRI Combination. *International Journal of Neuropsychopharmacology* **2017**, *20*, 919-927, 10.1093/ijnp/pyx060.
84. Mohan Pabba; Adrian Y.C. Wong; Nina Ahlskog; Elitza Hristova; Dante Biscaro; Wissam Nassrallah; Johnny K. Ngsee; Melissa Snyder; Jean-Claude Beique; R. Bergeron; et al. NMDA Receptors Are Upregulated and Trafficked to the Plasma Membrane after Sigma-1 Receptor Activation in the Rat Hippocampus. *The Journal of Neuroscience* **2014**, *34*, 11325-11338, 10.1523/jneurosci.0458-14.2014.
85. Hongling Zhang; Javier Cuevas; Sigma receptors inhibit high-voltage-activated calcium channels in rat sympathetic and parasympathetic neurons. *Journal of Neurophysiology* **2002**, *87*, 2867-2879, 10.1152/jn.2002.87.6.2867.
86. Lucile Noyer; Loic Lemonnier; Pascal Mariot; Dimitra Gkika; Partners in Crime: Towards New Ways of Targeting Calcium Channels. *International Journal of Molecular Sciences* **2019**, *20*, 6344, 10.3390/ijms20246344.
87. Jing Wang; Sylvia B. Smith; A Novel Mechanism of Sigma 1 Receptor Neuroprotection: Modulation of miR-214-3p. *Advances in Experimental Medicine and Biology* **2019**, *1185*, 463-467, 10.1007/978-3-030-27378-1_76.
88. Zhi-Fang Deng; Hui-Ling Zheng; Jian-Guo Chen; Yi Luo; Jun-Feng Xu; Gang Zhao; Jia-Jing Lu; Hou-Hong Li; Shuang-Qi Gao; Deng-Zheng Zhang; et al. miR-214-3p Targets β-Catenin to Regulate Depressive-like Behaviors Induced by Chronic Social Defeat Stress in Mice. *Cerebral Cortex* **2018**, *29*, 1509-1519, 10.1093/cercor/bhy047.
89. Kiyoshi Matsuno; Tetsuya Kobayashi; Mihoko K. Tanaka; Shiro Mita; Sigma 1 receptor subtype is involved in the relief of behavioral despair in the mouse forced swimming test. *European Journal of Pharmacology* **1996**, *312*, 267-71, .
90. Weichen Song; Yifeng Shen; Yanhua Zhang; Sufang Peng; Ran Zhang; Ailing Ning; Huafang Li; Xia Li; Guan Ning Lin; Shunying Yu; et al. Expression alteration of microRNAs in Nucleus Accumbens is associated with chronic stress and antidepressant treatment in rats.. *BMC Medical Informatics and Decision Making* **2019**, *19*, 271-11, 10.1186/s12911-019-0964-z.