Literature Review

Sigma Receptors: Literature Review

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Abstract

The paper reviewed data confirming that sigma1 receptors modulate NMDA neurotransmission. It has been established that they can enhance the spontaneous release of glutamate in the hippocampus, potentiate the release of a neurotrophic factor induced by glutamate, and also participate in the processes of synaptic restructuring (facilitation of long-term potentiation) in the mammalian hippocampus. But the use of high doses of agonists or antagonists of sigma1 receptors in animal models does not have any effect on memory modulation or learning processes in control animals. These findings indicate that sigma1 receptors do not affect the physiological (normal) processes of memory consolidation. The effects of sigma1 receptors considered in the work speak of effects on cognitive processes only in conditions of neurotransmitter imbalance. In a number of works, with the participation of various experimental models, the possible involvement of sigma1 receptors in the processes of memory recovery was revealed. A real break-through in the treatment of affective disorders is being made in our time due to an increasingly detailed study of the mechanisms of intracellular receptor structures and chaperone proteins, in particular, sigma receptors. By acting on these mechanisms, side effects in the treatment of depression, inevitable with the use of traditional antidepressants, can be avoided. Also, thanks to modern drugs based on interaction with sigma receptors, it is possible to influence neurogenesis, learning and memory processes. Thus, the sigma-1 receptor is an extremely promising object that can be considered as a potential therapeutic target for the treatment of neuropathological diseases.

Keywords: Sigma1 Receptors; Models; Drugs

Introduction

Over the past decades, a special type of receptor, sigma, has attracted more and more attention from researchers. Initially, in 1976, they were described as a subtype of opioid receptors, but a little later it turned out that this is a special new type of receptor that is expressed in the cells of the brain, retina, lens, liver, and tumor cells. There are a number of studies confirming the fact that sigma receptors are involved in the formation of many neurological and psychosomatic conditions. A special place is given to the study of anxiety disorders, which, as a rule, are manifested by anxiety, a feeling of internal tension, as well as palpitations, shortness of breath and stabbing pains in the heart area [3,4]. The largest study

in 52 countries involving more than 29,000 patients confirmed the fact that psychosocial factors, including anxiety, are independent risk factors for cardiovascular disease, increase the incidence and mortality from coronary heart disease and significantly aggravate the course of cardiovascular diseases. The discovery of sigma receptors in cardiac cardiomyocytes has opened up new opportunities for scientists to study their participation both in the normal functioning of heart cells and in various disorders. Currently, the existence of two subtypes of sigma receptors is known, one of which (sigma 1) is found in the cardiomyocytes of the atria and ventricles of the heart of rats and guinea pigs, as well as in the cells of the conduction system [2].

Relevance

Sigma receptors are classified as a separate class of intracellular receptors. Among these receptors, sigma-1 is the best studied for pharmacological applications. Sigma-2 (σ2) is an endoplasmic receptor that is identified as the endoplasmic reticulum (ER) transmembrane protein TMEM97 [5,9,10]. This protein has gained scientific interest because of its role in the proliferative status of cells. Note that many tumor cells from different organs overexpress the σ2 receptor, and some σ2 ligands are cytotoxic provocateurs in (resistant) cancer cells. It is these data that have identified the σ2 receptor as a potential drug target that undergoes binding/activation for the diagnosis or therapy of tumors. Interestingly, a number of groups have also shown how the σ2 receptor can be used to transport anticancer drugs directly to tumors [9]. Oncology is a multifactorial pathology with multiple cell populations, so a polypharmacological approach is often needed. Instead of simultaneously administering different classes of drugs, now using a single molecule that interacts with different pharmacological targets, namely the multitasking targeted ligand (MTDL) [5,10], this innovation is a promising and currently implemented strategy that can overcome the pharmacokinetic problems associated with the administration of multiple molecules. Every day there is more evidence that sigma-2 ligands have the ability to treat cancer and Alzheimer's disease (AD), but the mechanisms linking these two diseases are unknown. Data obtained over the past few years in human and animal models show that cholesterol homeostasis is altered in Alzheimer's disease and cancer, highlighting the importance of cholesterol homeostasis in Alzheimer's disease and cancer [11].

Let's talk about sigma-1 receptors. This receptor binds a wide range of chemical compounds of various structural classes and various therapeutic and pharmacological properties. The sigma-1 receptor is a transmembrane protein of the endoplasmic reticulum (ER), where it regulates the function of the inositol-3-phosphate receptor, thus it stabilizes calcium signaling between the endoplasmic reticulum and mitochondria. This receptor is involved in the formation of a huge number of neurological and psychiatric conditions. It is supposed to act as a sensor for the normal functioning of calcium. In the past few years, many scientists have written that it plays a role in the disruption of calcium signaling in the pathogenesis of Alzheimer's and Huntington's diseases. In particular, changes in calcium homeostasis in the endoplasmic reticulum lead to disruption of synaptic connections in neurons [24].

Sigma1 receptors are located in the brain and spinal cord, liver, pancreas, adrenal glands, and lungs. In the brain, they are located unevenly - most of them in the hippocampus, amygdala, blue spot, red nuclei, frontal cortex and substantia nigra. Sigma1 receptors regulate ion channels, including potassium, calcium, and chloride, NMDA receptors, release of various neurotransmitters, lipid transport, brain-derived neurotrophic factor signal transduction, myelination, neuronal and synaptogenesis [4,6]. The moment of stabilization by sigma1 receptors of receptors on calcium ion channels in the endoplasmic reticulum is a key activator of three dehydrogenases in the tricarboxylic acid cycle. Among other things, it is a regulator of ATP production and energy within the cell. Many studies confirm that the activation of sigma1 receptors does not cause hyper- or hypo-activation of neuronal activity, but rather, it normalizes the dynamics of ions in neurons. Structurally, sigma1 receptors are integral membrane proteins with two transmembrane domains and a long C-terminus in the lumen of the endoplasmic reticulum. There are a lot of Sigma1 receptors in those areas of the endoplasmic reticulum membrane that are located close to the mitochondria [24].

The intraluminal domain of sigma1 receptors in the endoplasmic reticulum has a pronounced chaperone (protein) activity and prevents the formation of conglomerates of various proteins [12,13]. The mechanism of regulation of activation/inactivation of sigma1 receptors is associated with its chaperone activity: the inactive sigma1 receptor forms a protein complex with the EPR-specific BiP protein, which is extremely unique. The moment when sigma1 receptors bind to antagonists leads to the disconnection of sigma1 receptors and BiP, which in turn triggers the activation of the sigma1 receptor chaperone function. A number of psychotropic drugs, which include antidepressants (mostly fluvoxamine) and neurosteroids, activate sigma1 receptors, while the antipsychotic haloperidol and progesterone block their action. To date, a lot of evidence indicates a beneficial effect on cognitive functions, as well as the antidepressant effect of sigma1 receptor agonists [20]. Thus, the results of recent studies show the possibility of participation of cellular stress or EPR stress in the development of affective disorders. According to one professor, in this case, molecular

chaperones can serve as a target for therapeutic intervention. Another pharmacological feature of sigma1 receptors is their ability to "modulate" or "enhance" monoaminergic (serotonin and dopaminergic) or glutamatergic signaling. It can be concluded that substances that have the property of agonists of both sigma1 receptors and receptors of other systems (for example, 5-HT1A and muscarinic acetylcholine receptors) have an antidepressant and antiamnesic effect at lower doses than drugs that have an affinity for only one type of receptors [12,22,23].

Molecular chaperones (also known as "stress proteins") are proteins that regulate the formation of a three-dimensional structure, stabilize the conformation and/or correct folding of unfolded or misfolded some other proteins [1]. When the activity of molecular chaperones is disturbed or the number of misfolded proteins is exceeded, and the abilities of molecular chaperones cannot correct their structure, the proteins at this moment begin to form highly toxic complexes, which leads to cell dysfunction or apoptosis. Diseases associated with impaired protein coagulation/aggregation include Parkinson's disease, Alzheimer's disease, and type 2 diabetes mellitus [2,3]. In behavioral and electrophysiological studies, fluvoxamine contributed to the dissociation of sigma1 receptors and BiP, which led to the activation of the chaperone activity of sigma1 receptors and increased neuritogenesis, and an improvement in cognitive functions in animals was noted [4]. Based on such data obtained by neuroimaging methods, the professor hypothesized that fluvoxamine's predominant efficacy in the treatment of psychotic depression, a severe depressive episode in which delusional disorders are present, correlates not so much with serotonin transport, but with affinity for sigma1-receptors. In addition, in the light of the neuroprotective effect of sigma1 receptor agonists, the researcher suggested that their use should be effective in depression with comorbid vascular and/or neurological disorders that occur with memory and cognitive impairment. In a report on the clinical aspects of the use of one of the most potent sigma1 receptor agonists, the antidepressant fluvoxamine, a professor from the UK, in a report on the clinical aspects of the use of one of the most potent agonists of sigma1 receptors, the antidepressant antidepressant fluvoxamine, dwelled in detail on the historical aspects of the study of the pathogenesis of depression and especially the cognitive concept [16,17]. The author believes that one of the key links in the formation of depression is aberrant cognitive (pathology of thinking, in which the information

organization process suffers), as well as pathophysiological mechanisms of cognitive depressive disorders, this is supported by a number of neuroimaging experiments associated with the death of brain cells, which is proposed to be prevented in including with the help of sigma1 receptor agonists. Experiments involving animals have shown that the stimulating effect on sigma1 receptors is associated with neurogenesis (neuroplastic effect), a decrease in anxiety symptoms, an improvement in memory and learning, a decrease in stress and obsessive-compulsive symptoms. Fluvoxamine at a dose of 50-200 mg has a pronounced affinity for sigma1 receptors in the human brain [1]. Increased activation of serotonergic neurons in the dorsal raphe nucleus is a very important and powerful action of sigma-1 receptors. Activation of serotonergic transmission under the influence of such agonists begins after two days of treatment, while clinically significant changes induced by inhibition of serotonin reuptake appear only after two to three weeks of antidepressant administration [11,20]. The rapid serotonergic effect of sigma-1 receptor agonists implies an earlier onset of antidepressant action compared to traditional antidepressants. Moreover, the combination of the selective sigma-1 receptor agonist pramipexole and the antidepressant sertraline at subeffective doses in an experimental model of depression demonstrates a synergistic antidepressant effect [1,2]. Unfortunately, it has not yet been possible to find out which symptoms of depression (cognitive impairment, hypothymia, anxiety) are the primary target for sigma1-receptor agonists, to what extent the clinical effect of antidepressants depends on synergistic interaction with sigma1- and monoaminergic receptors, what time is required for sigma1-agonists receptors to achieve a therapeutic effect and whether there are side effects that are often encountered with selective agonists. Such open questions imply an innovative nature of data on the role of sigma1 receptors in the formation of depressive symptom complex in general and cognitive disorders in particular, and this also speaks of the scientific and practical perspective that the results of the presented neuroimaging and clinical studies open up [8,9].

When there is a modulation of sigma-1 receptors on neurotransmitter systems, then the enhancement of glutamatergic, cholinergic, serotonergic neurotransmission is turned on. The opposite effect, when activation of sigma-1 receptors reduces the intensity of the release of norepinephrine and gamma-aminobutyric acid [20]. It is the increase or decrease in calcium current due to

the work of sigma-1 receptors that explains why selective sigma receptor agonists can modulate a wide range of neuronal effects, this also includes the key mechanism of the influence of sigma-1 receptors on learning and memory processes [21].

In addition to an understandable physical interaction, regulation of the activity of voltage-gated K+ channels in mouse nerve terminals of the posterior pituitary gland, the sigma-1 receptor contributes to the regulation of K+ channel activity in rat hippocampal sections, intracardiac neurons, and tumor cells. The sigma-1 receptor has ligands that modulate several types of presynaptic Ca^{2+} channels in rat sympathetic and parasympathetic neurons. The sigma-1 receptor also modulates the activity of the NMDA receptor and affects synaptic plasticity through low-conductivity Ca^{2+}-activated K+ channels [15,16]. Using HEK293 and COS-7 cells, neonatal mouse cardiomyocytes, it has been shown that the sigma-1 receptor modulates cardiac voltage-gated channels of sodium Na+ ions [1,4,5]. Calcium ion currents are inhibited in cultured retinal ganglion cells under the influence of the sigma-1 receptor agonist SKF10047. An interesting relationship between the sigma-1 receptor and the L-type Ca^{2+} channel was proven using immunoprecipitation [17]. There is evidence that the sigma-1 receptor regulates neurotransmitter dispatch in dopamine, serotonin and m-cholinergic transmission, is involved in cell differentiation, the cellular response to inflammation, and in the pathogenesis of extrapyramidal disorders. Interestingly, the sigma-1 receptor was found in the extracellular space in NG-108 cells exposed to cocaine, demonstrating intermittent activity of the sigma-1 receptor as a chaperone in the extracellular space as well [18,19].

An impressive decrease in the number of NMDA receptors in the prefrontal cortex and hippocampus is noted in people with depression. An experimental model of depression has been performed (ectomy of the olfactory bulbs in rats leading to a decrease in the number of NMDA receptors) accompanied by a behavioral abnormality that resembles psychomotor agitation, loss of interest and cognitive dysfunction in clinical depression. Sigma-1 receptor agonists improve behavioral deficits and also increase NMDA receptor expression [8]. These astonishing findings support a link between depression and two types of receptors: NMDA and sigma-1. Together with the modulating role of receptors in glutamatergic and serotonergic transmission, which is associated with depression, sigma receptors have an additional mechanism of action associated with neuroplasticity processes. It has been found that a mutation in the E102Q receptor leads to an autosomal recessive form of juvenile paralysis. With the development of this disease, the motor neurons of the spinal cord die. Mutated mice with a deletion of the sigma-1 receptor gene that exhibit symptoms of paralysis have a significantly reduced lifespan, and the onset of paralysis symptoms is much earlier than in mice expressing the sigma-1 receptor [10,12,13]. This indicates that even in mice, this receptor slows down the development of degenerative processes. Earlier works showed that two types of potassium channels are located in the postsynaptic membrane of cholinergic synapses of motoneurons: Kv2.1 and SK [13]. These channels remove potassium ions K+ from the cell and this ensures a decrease in the excitability of motor neurons, which is extremely important, since motor neurons die first under stress [26].

The sigma-1 receptor can interact with the inositol triphosphate receptor, which is located on the membrane of the endoplasmic reticulum, receptor activators at this moment lead to a significant increase in the release of calcium from the endoplasmic reticulum into the cytosol. Calcium activates calmodulin, calmodulin in its active form directly opens the channel of potassium ions SK in the plasma membrane. Calmodulin is able to influence the Kv2.1 channel through the activation of calcineurin, which causes dephosphorylation of the channel and leads to its further activation [18]. In general, both potassium channels can be modulated by activation of the sigma-1 receptor through a cascade of protein interactions. In mice, injection of amyloid peptide activates the sigma-1 receptor, thus reducing the symptoms of Alzheimer's disease, significantly improving memory test results. Studies using positron emission tomography have shown that the sensitivity of sigma-1 receptors does not change during normal aging [20]. This is in contrast to the age-dependent decline in cholinergic, glutaminergic and dopaminergic reception. But Alzheimer's patients showed a decrease (26% loss) of sigma-1 receptors in the CA1 region of the hippocampus compared to healthy individuals. Moreover, this decrease was correlated with the degradation of pyramidal neurons. It has recently been found that agonists of these receptors can counteract microglial activation [21,22]. As a result, the inflammatory component of neurodegenerative diseases is attenuated.

Sigma receptors affect not only memory, emotions, sensory perception and fine motor skills, but also drug addiction. Endogenous ligands of sigma-1 receptors are neurosteroids (progesterone), but also dimethyltryptamine, which provides modulation of Na-channels by sigma-1 receptors [23,25]. Clinical data were obtained through already known physiological mechanisms, such as migration to the region of the outer neuronal membrane as part of lipid rafts (neuroprotective effect), stimulation of the synthesis of nerve growth factor NGF, activation of sprouting (neuroplastic effect), stimulation of the synthesis of the brain-derived neurotrophic factor BDNF (neurotrophic effect), regulation of potassium, calcium, sodium and chloride ion channels, elimination of an imbalance in the work of NMDA receptors, serotonin, dopamine receptors (modulating effect), translocation with a single administration of ligands (non-modulating effect [26]. This once again confirms that with the help of sigma-1 receptor agonists and antagonists can influence learning and memory processes in neurotransmitter imbalance, behavioral processes in schizophrenia, have antidepressant and anxiolytic effects, and cause analgesia. Thus, clinical medicine, based on data from studies of the structure and properties of sigma-1 receptors, gains the possibility of effective physiologically based correction of a number of pathological conditions (depressive states, neurodegenerative diseases, behavioral Alzheimer's disease, and others).

One of the main factors in the formation of depression and cognitive decline in the elderly are the physiological processes of brain aging, as well as age-dependent somatic diseases. Physiological aging is associated with changes in the metabolism of biological amines (serotonin, dopamine, norepinephrine), which leads to a decrease in their concentration [3,6,7,14,15]. The age-related reduction of cerebral blood flow in the prefrontal and limbic regions in elderly depressed patients explains this mechanism. It is these age-related changes that can be considered as the main target for the neuroprotective effects of sigma1 receptor agonists [18,19].

Research and Models

A huge number of preclinical studies, the data of these studies, which were conducted on various models of memory impairment, allow us to consider sigma-1 receptor agonists as promising future drugs for the treatment of cognitive dysfunction, so the regulation of neuronal plasma membrane excitability through the sigma-1 receptor plays a key role in preventing neurological

diseases. We found that since the sigma-1 receptor binds a wide range of chemical compounds of various structural classes and various therapeutic properties, it is of great interest not only for pathological physiology, but also for pharmacology [2,3]. Employees of the laboratory of molecular neurodegeneration of Peter the Great St. Petersburg Polytechnic University adhere to the calcium hypothesis of the development of neuropathology. According to the hypothesis, it is the violation of calcium signaling that contributes to the development and emergence of neurodegenerative diseases. Do not forget that the sigma-1 receptor regulates the function of the inositol triphosphate receptor, thus stabilizing calcium signaling between the endoplasmic reticulum and mitochondria. Our interest in studying the sigma-1 receptor is due to its biophysical role in the formation of neurological and psychiatric conditions, as well as in the regulation of intracellular calcium ion concentration and calcium signaling [3,4].

In an attempt to understand and also explain the physiological significance of the balance of oligomeric and monomeric forms of the sigma-1 receptor, it has been proposed that oligomerization of the sigma-1 receptor regulates its ligand-mediated functions. Presumably, ligands of the sigma-1 receptor can influence the kinetics of interaction of the receptor with other so-called client proteins (ion channels and others) by changing the ratio between oligomeric and monomeric forms, shifting the balance in favor of the former. To date, the sigma-1 receptor is presented as a highly dynamic molecule capable of forming homomeric complexes, which provide the multitasking functions of the receptor in order to more accurately answer questions about the localization and organization of the ligand-binding site, as well as determine the stoichiometry of binding of various ligands to the sigma-1 receptor, additional studies are required using high-precision methods of structural biology, such as X-ray diffraction analysis and NMR spectroscopy [12,18].

Conclusions

The paper reviewed data confirming that sigma1 receptors modulate NMDA neurotransmission. It has been established that they can enhance the spontaneous release of glutamate in the hippocampus, potentiate the release of a neurotrophic factor induced by glutamate, and also participate in the processes of synaptic restructuring (facilitation of long-term potentiation) in the mammalian hippocampus [1]. But the use of high doses of agonists

or antagonists of sigma1 receptors in animal models does not have any effect on memory modulation or learning processes in control animals. These findings indicate that sigma1 receptors do not affect the physiological (normal) processes of memory consolidation. The effects of sigma1 receptors considered in the work speak of effects on cognitive processes only in conditions of neurotransmitter imbalance [4,7]. In a number of works, with the participation of various experimental models, the possible involvement of sigma1 receptors in the processes of memory recovery was revealed. A real breakthrough in the treatment of affective disorders is being made in our time due to an increasingly detailed study of the mechanisms of intracellular receptor structures and chaperone proteins, in particular, sigma receptors [12]. By acting on these mechanisms, side effects in the treatment of depression, inevitable with the use of traditional antidepressants, can be avoided. Also, thanks to modern drugs based on interaction with sigma receptors, it is possible to influence neurogenesis, learning and memory processes. Thus, the sigma-1 receptor is an extremely promising object that can be considered as a potential therapeutic target for the treatment of neuropathological diseases.

Bibliography

1. Emanuela Arena., *et al*. "Novel Sigma-1 receptor antagonists: from opioids to small molecules: what is new?" *Future Medicinal Chemistry* 10.2 (2018): 231-256.

2. Huan Yang., *et al*. "SIGMAR1/Sigma-1 receptor ablation impairs autophagosome clearance". *Autophagy* 15.9 (2019): 1539-1557.

3. Zhenjiu Wang., *et al*. "Phases of the (2+1) Dimensional SO (5) Nonlinear Sigma Model with Topological Term". *Physical Review Letters* 126.4 (2021): 045701.

4. Sławomir J Grabowski., *et al*. "Are Various σ-Hole Bonds Steered by the Same Mechanisms?" *Chemphyschemistry* 18.12 (2017): 1569-1577.

5. Ai-Fang Chen., *et al*. "Sigma-2 Receptor as a Potential Drug Target" 28.21 (2021): 4172-4189.

6. Mireia Herrando-Grabulosa., *et al*. "Sigma1 receptor as a therapeutic target for amyotrophic lateral sclerosis". *British Journal of Pharmacology* 178.6 (2021): 1336-1352.

7. Manuel Merlos., *et al*. "Sigma-1 Receptor and Pain". *Handbook of Experimental Pharmacology* 244 (2017): 131-161.

8. Francesca Serena Abatematteo., *et al*. "σ 2 Receptor and Its Role in Cancer with Focus on a MultiTarget Directed Ligand (MTDL) Approach". *Molecules* 26.12 (2021): 3743.

9. Kai Yang., *et al*. "Sigma-2 Receptor-A Potential Target for Cancer/Alzheimer's Disease Treatment via Its Regulation of Cholesterol Homeostasis". *Molecules* 25.22 (2020): 5439.

10. Assaf Alon., *et al*. "Structures of the σ 2 receptor enable docking for bioactive ligand discovery". *Nature* 600.7890 (2020): 759-764.

11. Lin Guo and Xuechu Zhen. "Sigma-2 receptor ligands: neurobiological effects". *Current Medicinal Chemistry* 22.8 (2015): 989-1003.

12. Renzo Mancuso and Xavier Navarro. "Sigma-1 Receptor in Motoneuron Disease". *Advances in Experimental Medicine and Biology* 964 (2017): 235-254.

13. Pasquale Linciano., *et al*. "Sigma-1 receptor antagonists: promising players in fighting neuropathic pain". *Pharmaceutical Patent Analyst* 9.3 (2020): 77-85.

14. Cristina Sánchez-Fernández., *et al*. "Sigma-1 Receptor Antagonists: A New Class of Neuromodulatory Analgesics". *Advances in Experimental Medicine and Biology* 964 (2017): 109-132.

15. Eduardo E Benarroch. "Sigma-1 receptor and amyotrophic lateral sclerosis". *Neurology* 91.16 (2018): 743-747.

16. Saïd Kourrich. "Sigma-1 Receptor and Neuronal Excitability". *Handbook of Experimental Pharmacology* 244 (2017): 109-130.

17. Benjamin E Blass and John Patrick Rogers. "The sigma-2 (σ-2) receptor: a review of recent patent applications: 2013-2018". *Expert Opinion on Therapeutic Patents* 28.9 (2018): 655-663.

18. Tangui Maurice and Nino Goguadze. "Sigma-1 (σ1) Receptor in Memory and Neurodegenerative Diseases". *Handbook of Experimental Pharmacology* 244 (2017): 81-108.

19. Yakup Albayrak and Kenji Hashimoto. "Sigma-1 Receptor Agonists and Their Clinical Implications in Neuropsychiatric Disorders". *Advances in Experimental Medicine and Biology* 964 (2017): 153-161.

20. Yu Cai., *et al*. "Role of Sigma-1 Receptor in Cocaine Abuse and Neurodegenerative Disease". *Medicine and Biology* 964 (2017): 163-175.

21. Luana Naia., *et al*. "The Sigma-1 Receptor Mediates Pridopidine Rescue of Mitochondrial Function in Huntington Disease Models". *Neurotherapeutics* 18.2 (2021): 1017-1038.

22. Julian Wilke., *et al*. "Discovery of a σ 1 receptor antagonist by combination of unbiased cell painting and thermal proteome profiling". *Cell Chemical Biology* 28.6 (2021): 848-854.

23. Emanuele Amata., *et al*. "Novel Sigma Receptor Ligand-Nitric Oxide Photodonors: Molecular Hybrids for Double-Targeted Antiproliferative Effect". *Journal of Medicinal Chemistry* 60.23 (2017): 9531-9544.

24. Kristoffer Sahlholm., *et al*. "Sigma-2 receptor binding is decreased in female, but not male, APP/PS1 mice". *Biochemical and Biophysical Research Communications* 460.2 (2015): 439-445.

25. Maria Laura Pati., *et al*. "Quantum Dot Based Luminescent Nanoprobes for Sigma-2 Receptor Imaging". *Molecular Pharmaceutics* 15.2 (2018): 458-471.

26. Valentina Sabino and Pietro Cottone. "Sigma Receptors and Alcohol Use Disorders". *Handbook of Experimental Pharmacology* 244 (2017): 219-236.