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Review of Sigma Receptors

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Abstract (12 pt, bold)
Sigma receptors, unique receptors generally identified and classified as opioid and phencyclidine (PCP) receptors, are small membrane proteins concerned in several path physiological conditions, including cancer, drug addiction, and psychosis; thus, small molecule inhibitors of sigma receptors have been suggested as potential pharmacotherapeutics for these diseases. Two subtypes of the sigma receptor have been defined, termed sigma-1 and sigma-2, which can be distinguished by their pharmacological profiles, functions, molecular weight, locations selectivity, and subcellular. Sigma-1 receptor basically show modulatory properties, for example, modulation of chloride (Cl^-), calcium (Ca^{2+}), sodium (Na^+), potassium (K^+), compartmentalization of lipid on the endoplasmic reticulum, "ligand-operated" chaperoning activity at MAM, and sigma-1 receptor binding of cholesterol in lipid rafts regarding the proliferation of cancer cells. In this article we provide an overview of the present understanding of sigma receptor, focusing on binding and synthesis of sigma ligands, characterization binding site on the sigma-1 receptor, Probing the steroid binding domain-like I and II, and evidence of receptor dimmers.
Keywords: Sigma receptor, modulation, binding site, binding affinity

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Introduction

1. 1. **Identification and history overview discovery of sigma receptor**

Sigma receptors, at the beginning described as a subtype of opioid receptors, whiles they are considered unique receptors, now (Cobos, et al.,2008). Sigma-1 receptors are located in subcellular membranes and in the plasma membrane, certainly in the endoplasmic reticulum, where they affected as a modulator in intracellular Ca^{2+} signaling. Sigma receptor subtypes, sigma-1 and sigma-2, have been displayed to exist in a number of human tumor cell lines and rodent. However, their function is unknown and their expression is heterogeneous, sigma receptors have been suggested as potential targets for diagnostic tumor-imaging agents. Mach et al. (Mach, et al.,1997) in their studies shown that the sigma-2 subtype is upregulated in proliferative cells where the density of sigma-2 receptors was found to be 10-fold higher than in quiescent cells. It is already known that receptors have distinction anatomical distribution, particular drug selectivity patterns, and distinctive properties which are changed from opioid and other recognized neurotransmitter and hormone receptor families.

In 2009, Fontanilla et al. (Fontanilla, et al.,2009) in their studies presented that the sigma-1 receptor has been considered to be an orphan receptor. Nevertheless, the lack of selective sigma agents and the simultaneous use of different protocols led to inconsistent findings for more than a decade(Quirion, et al.,1987). Consequently, interest in sigma receptor research decreased until the early 1990's, when the two pharmacologically and functionally subtypes, sigma-1 and sigma-2, were recognized, renovating interest in these proteins(Quirion, et al.,1992). The sigma-1 receptor shares 95% similarity and 90% identity across species, and the guinea pig receptor shares 67% similarity and 30% identity with the yeast enzyme ergosterol C8-C7 isomerase (ERG2), and displays no homology with other mammalian proteins, so the belonging of sigma receptors to the family of sterol isomerases was suggested(Moebius, et al.,1997).

The sigma-1 receptors are dispersed in many peripheral tissues of immune systems and the endocrine (e.g., spleen, testis, adrenal gland, blood leukocytes, and ovary) (Chen, et al.,2007) but their concentration are high in the CNS (particularly in regions, which are associated with motoric, cognitive and sensoric functions) (Bouchard and Quirion,1997, Walker, et al.,1990). Besides, large amounts of it were discovered in some tissues and organs in the periphery such as the liver (Samovilova, et al.,1988), eye (Shamsul Ola, et al.,2001), kidney (Zhao, et al.,2005) and the heart (Ela, et al.,1994) as well as in some human tumor cell lines.

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Although there have been many reports on the possible role of sigma receptors recently, there is comparatively little information about the structure of the sigma receptor or its ligand binding site (Chen, Hajipour, Sievert, Arbabian and Ruoho,2007). Sigma-1 receptor binding investigations have discovered high affinities for a diversity of naturally occurring compounds such as neuropeptides and steroids. The sigma-1 and sigma-2 receptors are unique non-opioid and non-phencyclidine binding sites ubiquitously expressed in numerous tissues that are different from other known hormone receptors or neurotransmitters (see review (Su, et al.,2010) and (Aydar, et al.,2004, Bermack and Debonnel,2005, Bowen,2000, Seth, et al.,1997, Walker, Bowen, Walker, Matsumoto, De Costa and Rice,1990, Wheeler, et al.,2000)). The sigma-2 receptor has been proposed to be a talented target for pharmacological interferences to curb tumor progression (Hajipour, et al.,2011). Sigma-1 receptors are unusual receptors with possibly two transmembraneareas. Antagonists need doses meaningfully higher than their published affinities to have biological effects (Brimson, et al.,2011).

The studies of appreciative of the sigma-1 receptor have been a time-consuming, covert and as yet unfinished journey. The receptor has generally been investigated within the CNS. Nevertheless, more recent paper over the past decade has revealed the receptor to be plentiful in non-neuronal and neuronal tissues (Vilner, et al.,1995) leading to its study in cancer biology (Spruce, et al.,2004). Later the discovery of sigma receptors, primary interest was created by the proof that several antipsychotic agents shown affinity for this protein and sigma selective ligands might have helped as new antipsychotic drugs. Nevertheless, the lack of selective sigma agents and the simultaneous use of diverse protocols led to inconsistent findings for over a decade.

At the beginning, sigma receptors were suggested as a subtype of opioid receptor by Martin et al. (Martin, et al.,1976). Later studies revealed that they are distinctive proteins highly preserved across organelles, species, and cell types (Hanner, et al.,1996, Kekuda, et al.,1996, Mei and Pasternak,2001, Seth, et al.,1998, Seth, Leibach and Ganapathy,1997). Sigma receptors are broadly dispersed in the body (Hellewell, et al.,1994, Novakova, et al.,1995, Wolfe Jr, et al.,1997, Wolfe, et al.,1989). In the brain, sigma respecters are found in significant densities in endocrine and limbic areas that have been implicated in the pathophysiology of depression (Aan Het Rot, et al.,2009, Drevets, et al.,2008). Sigma-1 receptors are broadly expressed in the brain, but concentrated in particular areas involved in memory, sensory and emotion and motor functions (Bermack and Debonnel,2005, Guitart, et al.,2004, Monnet and Maurice,2006). In these investigations high to moderate levels of sigma-1 receptors were related with the hippocampus, particularly in the olfactory bulb, dentate gyrus, pons, hypothalamus, the central gray, several cortical layers, the septum, dorsal raphe, locus ceruleus, the red nucleus, the substantianigra pars compacta and various motor cranial nerve nuclei. The cerebellum is not especially enriched in sigma-1receptors, though several of its areas, for example the Purkinje cell layer, have been described to expression considerable concentrations of sigma-1receptors. Extra to the brain, sigma-1 receptors are also many in the spinal cord, mostly in the superficial layers of the dorsal horn (Alonso, et al.,2000).

1. 2. Subcellular distribution of sigma receptors

The subcellular distribution of sigma-1receptors was initially studied with radioligand binding in subcellular fractions, and recently with immunochemical methods. Binding investigates with the sigma-1radioligands [^{3}H](+)-pentazocine, [^{3}H](+)-3-PPP and [^{3}H](+)-SKF-10,047 revealed that sigma-1 receptors are situated in numerous types of rat, mouse and guinea pig brain membrane. These binding sites are more plentiful in microsomal membranes, which is consistent with the endoplasmic reticulum retention signal of the cloned sigma-1receptor (Hanner, Moebius, Flandorfer, Knaus, Striessnig, Kempner and Glossmann,1996, Seth, Leibach and Ganapathy,1997), but they are also existent in nuclear, synaptic and mitochondrial membranes (Cagnotto, et al.,1994, Cobos, et al.,2007, Dehaven-Hudkins, et al.,1994, Itzhak, et al.,1991). Immunohistochemical investigations further confirmed the presence of sigma-1 receptors in the endoplasmic reticulum not only in neurons (Alonso, Phan, Guillemain, Saunier, Legrand, Anoal and Maurice,2000), but also in many other cell

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types such as retinal cells (Jiang, et al.,2006), lymphocytes (Dussossoy, et al.,1999), certain cancer cells (Hayashi and Su,2005) and oligodendrocytes (Palacios, et al.,2003). Hayashi and Su by studying on NG108 cells showed that sigma-1receptors are situated as highly clustered globular structures enriched in cholesterol and neutral lipids in the endoplasmic reticulum and nuclear envelope (Hayashi and Su,2005). In neurons from the rat hippocampus and hypothalamus, electron microscopy studies revealed that sigma-1 receptor immunostaining was generally associated with the membrane of mitochondria, neuronalperikarya, some cisternae of the endoplasmic reticulum and dendrites, where it was localized in the limiting plasma membrane including the postsynaptic thickening (Alonso, Phan, Guillemain, Saunier, Legrand, Anoal and Maurice,2000). Sigma receptors are also small membrane proteins implicated in several pathophysiological conditions, including psychosis, cancer, and drug addiction; therefore, small molecule inhibitors of sigma receptors have been suggested as potential pharmacotherapeutics for these diseases (Chu, et al.,2011).

According to cell types, the sigma-1 receptor has been confined to diverse subcellular regions, including MAM (Hayashi and Su,2007), at the plasma membrane (Aydar, et al.,2002), ER (Ha, et al.,2011, Hayashi and Fujimoto,2010), in focal adhesion contacts (Mavlyutov and Ruoho,2007), the ER cisternae proximal to the plasma membrane (Mavlyutov, et al.,2010), and at the nuclear membranes (Jiang, Mysona, Dun, Gnana-Prakasam, Pabla, Li, Dong, Ganapathy and Smith,2006). The overabundance of physiological outcomes consequential from treatments with sigma receptor ligands may be described by the distinction subcellular localization and wide-ranging tissue distribution of the sigma-1 receptor (Su, Hayashi, Maurice, Buch and Ruoho,2010). Other pharmacological investigations have shown that sigma-1 receptor also binds a wide range of compounds including antidepressants, beta-adrenergic receptor ligands, antipsychotics, anti-histamines, neuropeptides, cocaine and cocaine analogs, PCP-like compounds, serotonergic compounds, neurosteroids, and opiates (Hajipour, et al.,2010).

1. 3. Cloning and structure of sigma-1 receptors

One of the differ that was distinguished between the two receptors subtypes is molecular weight: Hanner et al. shown that the sigma-1 receptor is a 29-kDa single polypeptide early cloned in guinea-pig liver (Hanner, Moebius, Flandorfer, Knaus, Striessnig, Kempner and Glossmann,1996), and later in the rat and mouse brain, a JAR human choriocarcinoma cell line, and in mouse kidney (Guitart, Codony and Monroy,2004), while sigma-2 receptors have not yet been cloned and have an apparent molecular weight of 18-21.5 kDa according to photo labeling studies (Hellewell, Bruce, Feinstein, Orringer, Williams and Bowen,1994, Pal, et al.,2007). This means that between two sigma receptors subtypes only the sigma-1 receptor has been cloned. The human sigma-1 receptor is a unique protein composed by 223 amino acids, and displays the typical sigma-1 binding profile which was first cloned and functionally expressed by Kekuda et al. (Hanner, Moebius, Flandorfer, Knaus, Striessnig, Kempner and Glossmann,1996, Kekuda, Prasad, Fei, Leibach and Ganapathy,1996, Seth, Fei, Li, Huang, Leibach and Ganapathy,1998). Noteworthy progress in current information of receptors was made when the sigma-1 receptor was cloned. The amino acid sequence of the sigma-1 receptor cloned from the human cell line ratio to the sigma-1 receptor cloned from the other species is highly homologous (Seth, et al.,2001), and does not any homology or even similarity with other mammalian proteins, but shares 30.3% identity with the yeast gene that encodes the C7–C8 yeast enzyme ergosterol (ERG2) (Moebius, et al.,1997), and contains an endoplasmic reticulum retention signal at the NH_2 terminus (Hanner, Moebius, Flandorfer, Knaus, Striessnig, Kempner and Glossmann,1996, Seth, Leibach and Ganapathy,1997).

Numerous structures have been suggested for sigma-1 receptors. First investigations suggested a single transmembrane domain structure (Dussossoy, Carayon, Belugou, Feraut, Bord, Goubet, Roque, Vidal, Combes and Loison,1999, Hanner, Moebius, Flandorfer, Knaus, Striessnig, Kempner and Glossmann,1996). In the recent years, Aydar and coworkers offered evidence that the sigma-1 receptor in the plasma membrane when expressed in Xenopuslaevisoocytes has two transmembrane segments

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with the NH_2 and COOH termini on the cytoplasmic side of the membrane (Aydar, Palmer, Klyachko and Jackson,2002). Recently, In several studies suggested that in addition to the hydrophobic regions that constitute the putative transmembrane domains, there are two additional hydrophobic segments that one of them partially overlapping the second transmembrane domain, which were suggested to be steroid binding domain-like sites (Chen, Hajipour, Sievert, Arbabian and Ruoho,2007), and proposing the existence of two different domains for ligand binding in the sigma-1 receptor (Bowen, et al.,1989, Pal, Hajipour, Fontanilla, Ramachandran, Chu, Mavlyutov and Ruoho,2007).

The sigma-1 receptor has been cloned from several tissues and species, and its predicted 223 amino acid sequence shares no homology with any other mammalian protein (Kekuda, Prasad, Fei, Leibach and Ganapathy,1996). In contrast of sigma-1 respecter, the pharmacology of sigma-2 receptors remains less definite. The sigma-2 receptor has not been cloned and its sequence remains unknown, while its presence was definite by photo affinity(affinity chromatography technique) labeling to be a 21.5 kDa protein (Hellewell, Bruce, Feinstein, Orringer, Williams and Bowen,1994). Before long 1900, thereafter the sigma-1 respecter was isolated and cloned showing its difference from any other known mammalian protein. The sigma-1 receptor has been cloned from different mammalian species, including humans (Kekuda, Prasad, Fei, Leibach and Ganapathy,1996, Prasad, et al.,1998), guinea pigs (Hanner, Moebius, Flandorfer, Knaus, Striessnig, Kempner and Glossmann,1996), and mice (Pan, et al.,1998), rats (Mei and Pasternak,2001, Seth, Fei, Li, Huang, Leibach and Ganapathy,1998), and shares about 90% identity and 95% similarity across these species.

2. CLASSIFICATION AND FUNCTIONS OF SIGMA RECEPTORS

2. 1. Classification of sigma receptors

Martin et al. (Martin, Eades, Thompson, Huppler and Gilbert,1976) in their seminal investigations that involved racemic SKF 10,047 (which is a mixture of (-) and (+) forms of the drug) shown that this drug produces actions through at least three different sites. In one hand, the (+)-isomer of SKF 10,047, interacts with at least two sites: (a) phencyclidine binding sites within the ionosphere of the NMDA receptor (because of this interaction that the expression δ-phencyclidine (PCP) was widespread in the early 1980s) and (b) non-NMDA, non-opiate sigma site which nowadays retains the name of sigma. On the other hand, the (-)-isomer of SKF 10,047 interactions are attributable principally to the kappa type of opiate receptor and creates actions that are reversible by naloxone (Matsumoto, et al.,2003).

In spite the initially thought that the sigma receptors have been measured as opioid receptors, have been classification as different pharmacological entity and their role shown to be distinct to the role of the opioid receptors (Bowen,2000, Martin, Eades, Thompson, Huppler and Gilbert,1976, Maurice and Su,2009). According to the ligand selectivity in the binding examines, two subtypes, sigma-1 and sigma-2 receptors, were recognized (Bowen,2000, Hellewell, Bruce, Feinstein, Orringer, Williams and Bowen,1994, Maurice and Su,2009). By developing of sigma selective ligands, such as (+)-3-PPP (3-(3-hydroxyphenyl)-N-(1-propyl)piperidine) and (+)-pentazocine, DTG (1,3-di-o-tolylguanidine), endorsed sigma binding sites to be distinguished as a distinct receptor system (Walker, Bowen, Walker, Matsumoto, De Costa and Rice,1990). It was described that sigma-1 binding sites show stereospecificity towards dextrorotatory isomers of benzomorphans, while sigma-2 binding sites show reverse selectivity, i.e., levorotatory isomers show higher affinity than dextrorotatory isomers of ligands (Hellewell and Bowen,1990, Quirion, Bowen, Itzhak, Junien, Musacchio, Rothman, Tsung-Ping, Tam and Taylor,1992). Two subtypes of sigma respecters, sigma-1 and sigma-2, can be distinguished by several factors such as their pharmacological profiles, ligand selectivity, anatomical distribution, differing in size, binding studies(Guitart, Codony and Monroy,2004, Hayashi and Su,2007, Quirion, Bowen, Itzhak, Junien, Musacchio, Rothman, Tsung-Ping, Tam and Taylor,1992).

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2. 2. Functions of sigma-1 receptors

In several reviews the functional sigma receptors are studied, that this located throughout the brain and in many peripheral tissues (Aydar, Palmer and Djamgoz,2004, Guitart, Codony and Monroy,2004, Hayashi and Su,2004, Matsumoto, Liu, Lerner, Howard and Brackett,2003), both subtypes of sigma receptors play different functional roles and have distinct pharmacological characteristics.

In 2007, Hayashi and Su in their studies identified the sigma-1 receptor as a new ER chaperone (Hayashi and Su,2007). In the CNS the sigma-1 receptors are included various neurotransmitter systems, such as serotonergic, drenergic, glutamatergic, adopaminergic, and cholinergic systems (Hindmarch and Hashimoto,2010). There are several proofs that indicate the sigma-1 receptor playing an important role in the maintenance of cellular membrane potential via a direct and/or indirect modulation of various ion channels (Chu, et al.,2013) and in neuropsychiatric and neurodegenerative diseases(So sigma-1 Receptor ligands have been suggested and tried clinically for anxiety, schizophrenia, depression, learning and memory improvement, cocaine addiction, and drug abuse) (Cobos, Entrena, Nieto, Cendan and Del Pozo,2008, Ferorelli, et al.,2011). However, the functions of the sigma receptor are not fully understood. Numerouspapersprove that the sigma-1 receptor intracellular trafficking of galactosylceramide-enriched membrane microdomains (Hayashi and Su,2004), intracellular Ca^{2+} release (Hayashi, et al.,2000), and regulates voltage-gated potassium channels (Aydar, et al.,2000, Aydar, Palmer, Klyachko and Jackson,2002, Wilke, et al.,1999, Wilke, et al.,1999). This wide-ranging distribution of sigma-1 receptor such as in the brain, spleen, testis, ovary, adrenal gland, and blood leukocytes has led to speculation that sigma receptors can mediate numerous cellular functions containing inhibition of proliferative response to mitogens (Casellas, et al.,1994), neuroprotective effects (Contreras, et al.,1991, Lysko, et al.,1992, Pontecorvo, et al.,1991), and increasing extracellular acetylcholine levels (Matsuno, et al.,1993). The modulation of ion channels (largely voltage-gated K^+ channels) in the plasma membrane could be a rational mechanism to regulate membrane excitability (Morio, et al.,1994, Soriani, et al.,1999, Soriani, et al.,1998, Wilke, Lupardus, Grandy, Rubinstein, Low and Jackson,1999, Wilke, Mehta, Lupardus, Chen, Ruoho and Jackson,1999, Wu, et al.,1991) and modulation of the effects of cocaine (Mccracken, et al.,1999, Mccracken, et al.,1999, Menkel, et al.,1991, Witkin, et al.,1993).

More recently, studies of Hayashi and Su (Hayashi and Su,2007) on the sigma-1 receptor revealed that this subtype of sigma receptor has chaperone activity as a Ca^{2+} -sensitive and ligand-operated chaperone in making a complex with BiP/GRP78 at the ER/ mitochondrial interface, reliable with the earlier reported antiapoptoticnature and progrowth of the sigma-1 receptor . Both subtype of sigma receptors are proposed to have opposite cellular function because by treatment with antagonists for sigma-1 receptor and with sigma-2 receptor agonists for sigma-2 receptor, inhibition of the sigma-1 receptor and activation of the sigma-2 receptor were resulted in antiproliferative effects against cancer cells (Colabufo, et al.,2004). Accumulating evidence proposes that sigma-1 receptor shows an important role in neuronal plasticity, a process implicated in the pathophysiology of neuropsychiatric diseases, such as MDD, and schizophrenia. So, this subtype of sigma receptors agonists may serve as new therapeutic drugs to alleviate the accumulation of misfolded proteins in the brain (Duncan and Wang,2005, Hashimoto,2009, Hashimoto,2009, Hashimoto and Furuse,2012, Hashimoto and Ishiwata,2006, Hayashi and Stahl,2009, Hayashi and Su,2007, Hayashi, et al.,2011, Hindmarch and Hashimoto,2010, Ishikawa and Hashimoto,2010, Niitsu, et al.,2012, Stahl,2008, Yoshida, et al.,2012).

2. 3. Functions of sigma-2 receptors

In other hand, the sigma-2 receptors are less identified, in part because of the lack of high-affinity ligands, this protein has not yet been cloned, which mostly show a poor selectivity profile especially over sigma-1 receptors. These receptors are associated with disorders and functions such as anxiety (Sanchez, et al.,1997), drug abuse and epilepsy (Guitart, Codony and Monroy,2004, Maurice, et

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al.,2002), depression (Maurice and Su,2009, Volz and Stoll,2004), inflammation (Bourrie, et al.,2004) and Alzheimer's disease (Villard, et al.,2008). Also, cancer diagnosis and treatment is an area of great attention in recent sigma receptor investigation.

Supplementary studies have revealed that sigma ligands, particularly sigma-2 agonists, can inhibit propagation and induce apoptosis in mammary and colon carcinoma cell lines which give sigma ligands potential application as agents for the treatment of cancer (Crawford and Bowen,2002, Ostenfeld, et al.,2005). Current reports demonstrate that sigma-2 subtype in rat liver membranes are localized to lipid rafts and that activation of the sigma-2 results in increases in sphingosylphosphorylcholine and ceramide, which may affect on the apoptotic signal transduction from sigma-2 receptors(Crawford and Bowen,2002). Also, the sigma-2 receptor is emerging as an imperative player in tumor imaging efforts as sigma-2 receptors are extremely concentrated in tumor cells. It has also been revealed that sigma-2 receptor activation by non-selective and selective ligands triggers cell death in numerous tumors through a way involving reactive oxygen species and lysosomal membrane leakage (Ostenfeld, Fehrenbacher, Høyer-Hansen, Thomsen, Farkas and Jäättelä,2005). Function of sigma-2 receptors in depression is not as well well-defined as that of sigma-1, though one report proposes that the sigma-2 selective ligand siramesine (Lu 28–179; 19-[4[1-(4-fluorophenyl)-1H-indol-3-yl]-1-butyl]spiro[isobenzofuran-1(^{3}H),49-piperidine]) displays equivalent antidepressant action related to the recognized antidepressants citalopram and imipramine in a chronic mild stress model in mice (Sanchez and Papp,2000).

3. INTER CELL

3. 1. Sigma receptors and signal transduction

In the recent years, researchers attempted to understand the mechanism by which the cellular membrane electrical potential affects cancer cell growth and proliferation; for example, several reports presented that progression through the cell cycle is contingent upon the translocation of ions across the plasma membrane.

Hydropathy analysis of the sigma-1 receptor shows that it is transmembrane spanning receptor. sigma-1 receptors may undergo unidirectional translocation to the plasmalemma. Classical plasma membrane bound neurotransmitter receptors the sigma-1 receptor resides specifically at the endoplasmic reticulum(ER) mitochondrion interface called the mitochondria associated enoplasmic reticulum membrane, whereas Sigma-1 receptors reside at the MAM. Where their ability to act as chaperones for type 3 inositol-1,4,5-triphosphate (IP_3) receptors assists the maintenance of Ca^{2+} homeostasis under conditions of cellular stress. Coupling of the sigma-1 receptor with various ER and/or plasma membrane ion channels is associated with its ability to control the locomotor activity and cellular proliferation produced in response to sigma-1 receptor ligands. Nevertheless, both the broad tissue distribution and the ability to bind dissimilar classes of ligands permits the sigma-1 receptor to mediate various cellular events, such as regulation of compartmentalization of lipid on the endoplasmic reticulum (Hayashi and Su,2003), calcium release (Hayashi and Su,2001),modulation of potassium channels in tumor cells (Wilke, Mehta, Lupardus, Chen, Ruoho and Jackson,1999), and "ligand-operated" chaperoning activity at MAM (Hayashi and Su,2007). Several located mainly at ER mitochondrion contact show that sigma-1 subtype must be classify as a chaperone of inositol (Hanner, Moebius, Flandorfer, Knaus, Striessnig, Kempner and Glossmann,1996, Martin, Eades, Thompson, Huppler and Gilbert,1976, Tsai, et al.,2009) triphosphate receptor, ensuring proper ER-mitochondrial Ca^{2+} signaling and cell survival (Tsai, Hayashi, Mori and Su,2009).

Sphingolipids (Ramachandran, et al.,2009) and neurosteroids (steroid hormones which are produced within the brain)(Maurice, et al.,1999, Maurice, et al.,2001, Su, et al.,1988), interact with sigma-1 sites which are now considered as the release of various neurotransmitters including acetylcholine (Horan, et al.,2002, Junien, et al.,1991, Kobayashi, et al.,1996) and glutamate (Meyer, et al.,2002),

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intracellular calcium signaling (Hayashi and Su,2007), and regulateand modulate the activity of ligand-gated ion channels and voltage-regulated (Maurice and Su,2009).

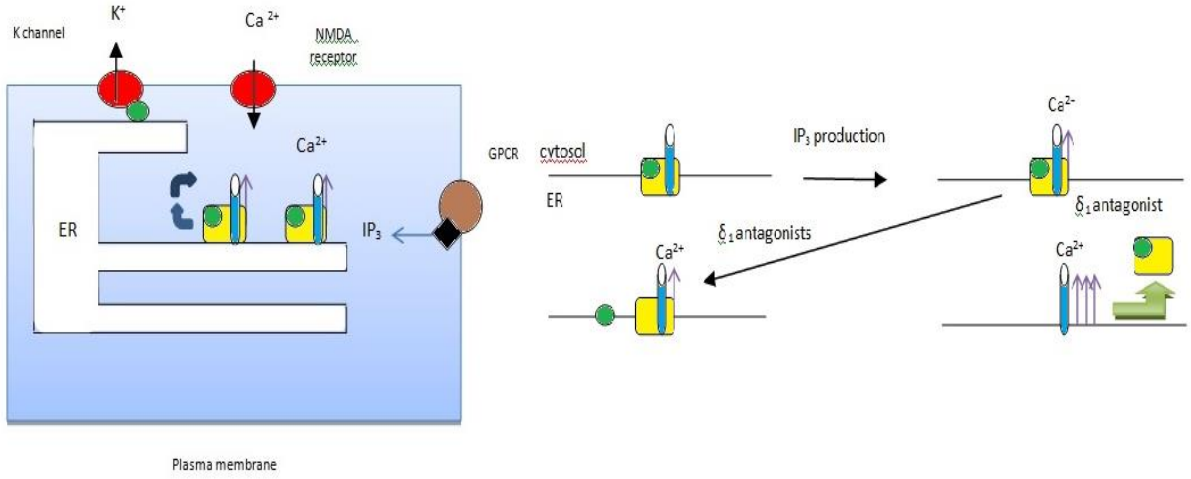

Fig. 1. Two schemes show the hypothetical function of sigma-1 receptors. Above: Under baseline (resting) conditions, sigma-1 receptors (green oval) largely reside at the ER, in connotation with ankyrin (yellow cuboid) and IP_3 receptors (blue bar). After agonist stimulation, sigma-1 receptors translocate to the plasmalemma where they can control ion channels (K^+ or NMDA receptor associated Ca^{2+}), perhaps by direct protein–protein interactions. Below: Sigma-1 receptor agonists induce dissociation and translocation of sigma-1 receptors plus ankyrin from the sigma-1 receptor–ankyrin IP_3 receptor complex. For this reason, both the binding of IP_3 to its receptor and Ca^{2+} efflux from the ER are increased. Sigma-1 antagonists induce dissociation of only sigma-1 receptors from the complex, ankyrin remaining in place. Antagonists do not affect Ca^{2+} release when given alone, but they impede the potentiation of Ca^{2+} efflux by sigma-1 receptor agonists (Cobos, Entrena, Nieto, Cendan and Del Pozo,2008, Hayashi and Su,2008).

Binding of ligand to the sigma-1 receptor has the following cellular signaling consequences: modulation of the interaction between an ER resident chaperone GRP78/BiP and sigma1 receptor-2 regulation of the association of ankyrin B, IP_3 receptor and sigma-1 receptor tricomplex (Coyle, et al.,1983), influencing the ion flux through different ion channels (Bartus, et al.,1982, Bergeron, et al.,1995, Bergeron, et al.,1996, Bergeron, et al.,1999, Bergeron, et al.,1993), redistribution of the sigma-1 receptor to different cellular locales(Couture and Debonnel,1998, Davies and Maloney, Debonnel, et al.,1996), and a reduction in the level of cellular oxidative stress (Debonnel, et al.,1996, Demerens, et al.,1999, Dong, et al.,2007). Therefore, inhibition of cell proliferation be due to pharmacological blockade of ion channel activity. The joining of the sigma-1 receptor to multiple ion channels may make available a mechanism by which sigma ligands are cytotoxic to cancer cells (Chu, Hajipour, Ramachandran and Ruoho,2011).

3. 2. Endogenous ligands of the sigma receptors

Despite years of study, the recognition of an endogenous ligand for these sites remains controversial (Guitart, Codony and Monroy,2004). Endogenous ligand is a ligand-activated molecular chaperone assisting the folding or unfolding and the assembly or disassembly of other signaling modulator [36]. In recent years, the subcellular location of this receptor is still under studying: while in 2002, Aydar et al. (Aydar, Palmer, Klyachko and Jackson,2002) demonstrate that plasma membrane localization of green fluorescent protein-labelled sigma-1 receptors, and in 2003, Hayashi and Su (Hayashi and Su,2003) demonstrate that equally compelling data for endogenous sigma-1 receptor in the endoplasmic reticulum. The endogenous ligand for the sigma-1 receptor has yet to be recognized. Neurosteroids, in certain progesterone, are the chief candidates for the endogenous ligand (Ramachandran, et al.,2008, Ramamoorthy, et al.,1995, Su, London and Jaffe,1988, Waterhouse and Lee Collier,1997).

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In 2009, N,N-dimethyltryptamine (DMT) has been suggested as the endogenous ligand by Fontanillaet et al. (Fontanilla, Johannessen, Hajipour, Cozzi, Jackson and Ruoho,2009). Fewnumber of endogenous small molecules bind to the sigma-1 receptor and have been presented to regulate its activity; these contain neurosteroid progesterone, testosterone, pregnonolone sulfate or possibly dehydroepiandrosterone (Su, London and Jaffe,1988) the hallucinogen DMT (Fontanilla, Johannessen, Hajipour, Cozzi, Jackson and Ruoho,2009, Johannessen, et al.,2008), and/or sphingolipids such as D-erythro-sphingosine (Ramachandran, Chu, Mavlyutov, Pal, Pyne and Ruoho,2009) and ceramides (Hayashi and Fujimoto,2010). Beside sneurosteroids, diverse classes of pharmacologic agents, including pimozide, imipramine, haloperidol, dextromethorphan, chlorpromazine, phencyclidine and propranolol have also been discovered to bind to the sigma receptor subtypes (Su,1982). The sigma-1 receptor ligands, containing DMT, at concentrations near to their K_i values, are measured as a reason of the dissociation of sigma-1 receptors from another ER chaperone, binding immunoglobulin protein (BiP), allowing sigma-1 receptors to chaperone inositol 1,4,5-trisphosphate receptors (IP_3Rs) at the MAM (Maisonial, et al.,2012). Greater than of normal concentrations of DMT are supposed as a reason of the translocation of sigma-1 receptors from the MAM to the plasma membrane, leading to the inhibition of voltage gated ion channels (Su, Hayashi, Maurice, Buch and Ruoho,2010).

Ramach and ran et al. (Ramachandran, Chu, Mavlyutov, Pal, Pyne and Ruoho,2009) and Hayashi and Fujimoto (Hayashi and Fujimoto,2010) in their studies had discovered that endogenous monochain N-alkyl sphingolipids, including N,N-dimethylsphingosine, sphinganine, and D-erythro-sphingosinebind to the sigma-1 receptor at relatively high affinity. This proposes that sigma-1 receptors are related with lipid containing micro-domains, where the receptor regulates lipid dynamics (Su, Hayashi, Maurice, Buch and Ruoho,2010). As well as, sigma-1 receptors are implicated in trophic factor signaling, cellular differentiation, ER lipid metabolism/transport, cellular protection, and lipid raft reconstitution at the plasma membrane (Hayashi and Su,2005, Hayashi and Su,2010). Be notable that sigma-1 receptors are efficient on the communication between lipids and cholesterol on the lipid raft, at the ER membrane (Hayashi and Su,2005, Hayashi and Su,2010, Su, Hayashi, Maurice, Buch and Ruoho,2010).

Studies of Su et al. had shown that particular gonadal and adrenal steroids, in certain PROG, bind to sigma receptors in the brain and spleen, proposing a link between the endocrine, nervous, and immune systems (Su, London and Jaffe,1988). In a following study, Maurice et al. (Maurice, et al.,1996) described on in vivo modulation of sigma-1 receptors in the mouse brain by neurosteroids, including DHEAS, PROG and PREG-S. DHEA, the most plentiful endogenous neurosteroid, is a sigma-1 receptor agonist with moderate affinity, whereas PROG and testosterone are sigma-1 receptor antagonists (Bhuiyan and Fukunaga,2011, Hayashi and Stahl,2009, Maurice, Urani, Phan and Romieu,2001, Waterhouse, et al.,2007). Also, PREG is a sigma-1 receptor agonist (Hayashi and Stahl,2009). These conclusions propose that, as endogenous sigma-1 receptor ligands, these neurosteroids have physiologically influence on both the peripheral and CNS systems (Maurice, et al.,2006, Maurice, Phan, Urani, Kamei, Noda and Nabeshima,1999, Maurice, Urani, Phan and Romieu,2001, Monnet and Maurice,2006, Niitsu, Iyo and Hashimoto,2012, Yoshida, Iyo and Hashimoto,2012).

Nevertheless, their affinities for this receptor seem to be too low for them to be endogenous ligands. The levels of physiological of progesterone during pregnancy can reach up to 400 nM; however, only 2% of this is free to pass the blood–brain barrier (Pardridge, et al.,1988, Schwarz, et al.,1989), consequential in only about 8 nM free progesterone that is capable to interact with sigma-1 receptors in the CNS (Schwarz, Pohl and Zhou,1989). In several reviews, the role of neurosteroids in depression (as sigma receptor effectors) has been studied (Dhir and Kulkarni,2008, Monnet and Maurice,2006, Van Broekhoven and Verkes,2003). Hereunto, the roles of other putative endogenous sigma ligands are unidentified (Fishback, et al.,2010).

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3. 3. Sigma receptors as modulators

According to their widespread modulatory role of sigma-1 receptor, this sigma receptor ligands have been suggested to be useful in a number of therapeutic fields such as cognitive deficits and amnesic, anxiety and depression, analgesia, schizophrenia, and against several effects of drugs of abuse such as methamphetamine and cocaine (Cobos, Entrena, Nieto, Cendan and Del Pozo,2008). Sigma-1 receptor ligands might change the location of action of sigma-1 receptor chaperones from the center of the cell to its periphery. Results of studies of Puente et al. identified that (have good agreement with previous model) identified that sigma-1 receptor as a constituent of the mechanisms modulating activity-induced sensitization in pain pathways (Puente, et al.,2009).

The modulation of ion channels in the plasma membrane can control the membrane excitability, and modulate the effects of cocaine (Cobos, Entrena, Nieto, Cendan and Del Pozo,2008). Sigma-1 receptor ligands have been described to modulate the release of several neurotransmitters and are under investigation for the treatment of a number of CNS disorders (Cobos, Entrena, Nieto, Cendan and Del Pozo,2008, Mishina, et al.,2008, Skuza,2003, Skuza and Rogoz,2005). Several papers have proposed that sigma-1 receptor basically show modulatory properties, for example, modulation of sodium (Na^+),chloride (Cl^-),potassium (K^+), and calcium (Ca^{2+})(Ding, et al.,2008, Johannessen, et al.,2009, Onkal and Djamgoz,2009, Renaudo, et al.,2007, Renaudo, et al.,2004) and sigma-1 receptor binding of cholesterol in lipid rafts (Palmer, et al.,2007) regarding the proliferation of cancer cells. In particular, the Na^+ channels are modulated by sigma-1 receptors and implicated in the adhesion, apoptosis and migration of cancer cells (Ding, Brackenbury, Onganer, Montano, Porter, Bates and Djamgoz,2008, Johannessen, Ramachandran, Riemer, Ramos-Serrano, Ruoho and Jackson,2009, Onkal and Djamgoz,2009).

Several investigates reported that sigma-1 modulate the function of various voltage-gated ion channels on the plasma lemma (Aydar, Palmer, Klyachko and Jackson,2002, Johannessen, Ramachandran, Riemer, Ramos-Serrano, Ruoho and Jackson,2009, Lupardus, et al.,2000, Tchedre, et al.,2008, Yamamoto, et al.,1995) and regulate intracellular calcium via interactions with IP_3 receptors on the ER (Hayashi, Maurice and Su,2000, Hayashi and Su,2001, Hayashi and Su,2007, Novakova, et al.,1998, Wu and Bowen,2008). Also, a new report details a chaperone-like activity for sigma-1 receptors, whereby its association with IP_3 receptors at the MAM facilitates efficient Ca^{2+} signaling from the ER to the mitochondria, proposing that sigma receptors show an important role in bioenergetics (Hayashi and Su,2007). The mediated modulation of ion channels in the plasma membrane can control the membrane excitability, and control the effects of cocaine (Cobos, Entrena, Nieto, Cendan and Del Pozo,2008).

The precise sigma-1 mediated signal transduction pathway is not identified yet. But it has been obviously shown that sigma-1receptors are neither tyrosine kinase receptors, soluble receptors, ion channel receptors nor classical G-protein coupled receptors (Aydar, Palmer and Djamgoz,2004, Hong and Werling,2000).

Sigma-1 and sigma-2 receptor are expressed in the periphery and in the CNS. It has been proposed that sigma-1 receptors are intracellular amplifiers for signal transduction systems (Su and Hayashi,2003). For instance, stimulation of sigma receptors amplifiesdo-paminergic, glutamatergic, IP_3-related metabotropic and nerve growth factor related signal transductions systems in vivo. Also, sigma receptors have been described to modulate calcium signaling at the endoplasmic reticulum, control neurotransmitter release, control cocaine dependent locomotor activity, change psychostimulant-induced gene expression and control IP_3 receptors (Cobos, Entrena, Nieto, Cendan and Del Pozo,2008, Guitart, Codony and Monroy,2004, Matsumoto, Liu, Lerner, Howard and Brackett,2003, Monassier and Bousquet,2002). Antonini and coworkers (Antonini, et al.,2011) suggest that agonist activation of sigma-1 receptors stabilizes inositol 1,4,5-triphosphate (IP_3) receptor conformation, leading to stabilization of Ca^{2+} signaling from the endoplasmic reticulum in to the mitochondria.

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Directly physical interactions between voltage-gated potassium channels and the sigma-1 receptor (Aydar, Palmer, Klyachko and Jackson,2002) and between the acid-sensing ions channel ASIC1a and the sigma-1 receptor (Carnally, et al.,2010) have been confirmed, leading to the proposition that the sigma-1 receptor may be a regulatory subunit for certain ion channels. Chu et al (Chu, Hajipour, Ramachandran and Ruoho,2011) in their studies reported that "in HEK-293 cells reconstituted with Kv1.4 potassium channel and the sigma-1 receptor, these derivatives were able to inhibit the outward current from the channel, consistent with sigma receptor modulation". Functional characterization of heptylamine and dodecylaminedisclosed that these molecules actively inhibit external current from the Kv1.4 potassium channel with relative IC_{50} values that correlate with the relative binding affinities at the sigma-1 receptor (Chu, Hajipour, Ramachandran and Ruoho,2011).

In this time, the sigma-2 receptors known less. It has been proposed that the sigma-2 receptor is able to modulation the apoptotic response of cells lines (Crawford and Bowen,2002) and the release of cellular calcium through an IP_3-independent mechanism (Vilner and Bowen,2000).

3. 4. Modulation of glutamate release by sigma-1 agonists

The neuro-transmitter glutamate, in addition to the known deficits of acetylcholine, can be reduced in AD. It is worth noting that acetylcholine and neuro-transmitter glutamate are supposed to play important roles in memory. Therefore, it is interesting that sigma ligands are able of modulating glutamate release in several areas of the brain.

In cultured hippocampal neurons, the sigma-1 receptor agonist (+)-pentazocine, but not the (−)-enantiomers of pentazocine and PREGS, and the neurosteroid PREGS that act as a sigma-1 receptor agonist, or the inactive steroid isopregnanolone increase the spontaneous release of glutamate. There are several factors that block this effect of PREGS: the sigma receptor antagonists BD1063 and haloperidol and a membrane-permeable calcium chelator. These observations propose that hippocampal glutamate release can be increased by activation of presynaptic sigma-1 receptors and a rising of the levels of intracellular Ca^{2+} (Meyer, Carta, Partridge, Covey and Valenzuela,2002). Later Dong et al have confirmed that the spontaneous release of glutamate is increased by PREGS both in prelimbic cortex and in the hippocampus, but not in the striatum. Sigma-1 receptors and alpha-1 adrenergicmediate the effect of PREGS in the prelimbic cortex, while the effect in the hippocampus is only dependent on sigma-1 receptors. As another results of their studies, one of the factors that plays a key role in the enhancement of glutamate release is intracellular calcium released from the endoplasmatic reticulum. As another neurosteroid with sigma-1 receptor agonist action, DHEA-S improves the spontaneous release of glutamate in prelimbic cortex and hippocampus.Sigma-1 receptors and dopamine D_1 mediate the effect of DHEA-S in the prelimbic cortex, while in the hippocampus occurs only by sigma-1 receptors (Dong, Cheng, Fu, Wang, Zhu, Sun, Dong and Zheng,2007).

Brain-derived neurotrophic factor (BDNF)-induced glutamate (that release in cultured cortical neurons) is potentiated by antidepressants with sigma-1 receptor agonist activity such as imipramine and fluvoxamine, and the sigma-1 receptor antagonist BD1047 blocked this potentiation. Both over expression of the sigma-1 receptor and pharmacological activation enhance BDNF-enhanced glutamate release. The sigma-1 receptor appears to play an significant function in BDNF signaling leading to the release of glutamate, and the improvement of glutamate release seems to occur by the PLC-gamma /IP_3/Ca^{2+} pathway (Yagasaki, et al.,2006).

Therefore, sigma ligands denote a strategy for modulating glutamatergic activity within the mammalian brain, and such modulation could be an extra mechanism fundamental the anti amnesic action of sigma-1 receptor agonists (Van Waarde, et al.,2011).

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3. 5. Modulation of the NMDA response by sigma-1 agonists

Sigma-1 receptors are capable to modulate several neurotransmitter systems. It has been reported that sigma-1 receptors can enhance cholinergic neurotransmission (for more information refer to (Bermack and Debonnel,2005, Monnet and Maurice,2006) and their references), enhance serotonergic neurotransmission (reviewed in (Bermack and Debonnel,2005)), potentiate glutamatergic neurotransmission (for more information refer to (Horan, Gifford, Matsuno, Mita and Ashby,2002, Maurice and Lockhart,1997) and their references), , negatively modulate the GABAergic system (Garrone, et al.,2000, Mtchedlishvili and Kapur,2003), modulate dopaminergic neurotransmission (reviewed in (Maurice, Martin-Fardon, Romieu and Matsumoto,2002)), and diminish nor adrenaline release (Campana, et al.,2002). In the dopaminergic system, direction of modulation of the dopaminergic system has been particularly controversial since the contradictory outcomes reported thus far make it hard to reach solid deductions. The conflicting results perhaps reflect the use of drugs with diverse routes of administration, and dissimilar degrees of selectivity for sigma-1 receptors(reviewed in(Maurice, Martin-Fardon, Romieu and Matsumoto,2002)).

Sigma-1 receptors have several the modulatory effects on different neurotransmitter systems, but the modulation of glutamatergic neurotransmission has been explored in greater detail than others. This effect has been reported that sigma-1 receptors can potentiate glutamate release induced by brain-derived neurotrophic factor (Yagasaki, Numakawa, Kumamaru, Hayashi, Su and Kunugi,2006), enhance spontaneous glutamate release in the hippocampus (Dong, Cheng, Fu, Wang, Zhu, Sun, Dong and Zheng,2007, Meyer, Carta, Partridge, Covey and Valenzuela,2002), facilitate long-term potentiation in the rat hippocampus (Chen, et al.,2006, Li, et al.,2006, Martina, et al.,2007), and potentiate the increase in $[Ca^{2+}]_i$ induced by glutamate in pyramidal neurons (Monnet, et al.,2003).

Among kainate, NMDA and AMPA-kainate receptors (these are the three subtypes of glutamate-gated ion channels), the connection between sigma-1 and NMDA receptors has been extensively explored, principally in studies of the NMDA-induced firing activity in the dorsal hippocampus. In these model sigma-1agonists such as (+)-pentazocineand the selective agonists JO-1784, the antidepressants clorgyline and sertraline, and the putative agonist DHEA were capable to modulate NMDA-induced firing. The effects of these ligands were reversed by known sigma-1antagonists such as NE-100 or BMY-14802, haloperidol, as well as by the putative endogenous ligand progesterone (extensively reviewed in (Bermack and Debonnel,2005, Monnet and Maurice,2006)). This is interesting to notice that in these studies sigma-1 agonists displayed a bell-shaped dose-response curve described by high-dose inhibition and low-dose stimulation. This type of dose-response curve showshormesis [18], and is well recognized for sigma-1 receptor activation, for example, in the modulation of NMDA-induced firing.

Mostly interesting are the investigations that related steroidal tonus under physiological conditions with the sigma-mediated potentiation of glutamatergic neurotransmission in the hippocampus. Studies show that this effect was affected by diminished levels of this neuro-steroid after ovariectomy (Bergeron, De Montigny and Debonnel,1996), and by increased levels of progesterone in pregnancy (Bergeron, De Montigny and Debonnel,1999). Recently, a molecular mechanism was proposed by which sigma-1receptor activation increases the NMDA receptor response. Ca^{2+} entering the cells through the NMDA receptors activates a Ca^{2+}-activated K^+ current, underlain by SK channels, which in turn shunts the NMDA receptor responses. Selective sigma-1 agonists prevented SK channel opening and consequently in-creased the NMDA receptor response, emphasizing the importance of the sigma-1receptor as a postsynaptic regulator of synaptic transmission (Martina, Turcotte, Halman and Bergeron,2007). Notably, the modulation of some neurotransmitter systems point out above may be a result, at least partially, of the modulation of NMDA receptors. In several review, it has been described in this connection that sigma-1 ligands can modulate cholinergic (Monnet and Maurice,2006), serotonergic (Takahashi, et al.,2001), dopaminergic (Maurice, Martin-Fardon, Romieu

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and Matsumoto,2002) or noradrenergic systems (Bermack and Debonnel,2005) through NMDA receptors.

NMDA receptors mediate the induction of long-term potentiation (LTP) and long-term depression in various brain areas (Artola and Singer,1993, Collingridge,1987, Izquierdo,1991). Such forms of synaptic plasticity are considered as significant cellular mechanisms underlying learning and memory (Frey and Morris,1997, Lynch,2004, Teyler,1987). In several researches, sigma-1 receptor agonists were exposed to modulate responses induced by NMDA receptor activation in several brain regions such as prefrontal cortex and the hippocampus. Sigma-1 receptor agonists potentiate some responses and inhibit others. When administered alone, sigma-1 receptor antagonists are without any effect, but these block the agonist-induced modulation.

As instance, the electrophysiological response of pyramidal neurons in the CA_3 region of the rat dorsal hippocampus to NMDA is potentiated by sigma-1 receptor agonists such as BD737, DTG, igmesine, (+)-pentazocine, DHEA, L687, or 384 and therapeutic drugs with significant sigma-1 receptor agonist affinity (the monoamine oxidase inhibitor clorgylineand the SSRI sertraline), while this potentiation is reversed by sigma-1 receptor antagonists such as NE-100, BMY14802, progesterone, haloperidol and testosterone (Bergeron, De Montigny and Debonnel,1995, Bergeron, De Montigny and Debonnel,1996, Debonnel, Bergeron and De Montigny,1996, Monnet, et al.,1992, Monnet, et al.,1992, Monnet, et al.,1990). Results of Bergeron et al. (Bergeron, De Montigny and Debonnel,1995) show that the potentiation continues for at least 1h and can be continued by prolonged micro ion to phoretic application of a sigma-1 receptor agonist; these observations confirmed that sigma-1 receptors do not rapidly desensitize.

Testosterone and progesterone (as steroid hormones with antagonist action) produce a tonic dampening of the role of sigma-1 receptors and, as a result of NMDA-mediated responses. Pregnancy decreases sigma-1 receptor role in the brain, because a tenfold higher dose of sigma-1 receptor agonists is needed to potentiate the NMDA response of pyramidal neurons in pregnant female rats than in non-pregnant control animals (Bergeron, De Montigny and Debonnel,1999).

Results of an electrophysiological study of Debonnel et al. (Debonnel, Bergeron, Monnet and De Montigny,1996) show that in the CA_3 region (on the intact side), JO-1784, (+)-pentazocine, neuropeptide Y and DTG induced a selective potentiation of NMDA-induced activation. On the lesioned side, the effect of (+)-pentazocine on the NMDA response was still present, but those of neuropeptide Y, JO-1784 and DTG were abolished. Also, these data were interpreted as proposing that the test drugs were acting on two different subtypes of sigma receptors, and that the receptors for igmesineand DTG are located on the mossy fiber terminals, in contrast to the receptors for (+)-pentazocineb.

In 1988, the effect of the intravenous administration of the sigma-2 subtype-selective ligand siramesine was assessed on the neuronal response to NMDA in the CA_3 region of the rat dorsal hippocampus. As a result, Siramesine was found to potentiate the NMDA response dose-dependently with a bell-shaped curve, but the effect of siramesine could – in contrast to the effect of sigma-1 receptor agonists – not be reversed by progesterone, haloperidol or NE-100. As another results, these data propose that, similarly to sigma-1 ligands, sigma-2 agonists potentiate the NMDA response and that the co-activation of sigma-1 and sigma-2 receptors could be necessary to induce an epileptoid activity (Couture and Debonnel,1998). Therefore, both subtype of sigma receptors appears to be involved in modulation of the NMDA response.

Bell-shaped dose–response curves are a public finding in researches regarding the effect of sigma-1 receptor agonists. At higher dose the potentiation is reversed but at low doses the NMDA response is potentiated (Bergeron, De Montigny and Debonnel,1995, Bergeron, Debonnel and De Montigny,1993, Monnet, et al.,1996, Monnet, Debonnel and De Montigny,1992). One of example for this is that the

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sigma-1 receptor agonist SR 31742A increases NMDA-induced inward currents of pyramidal cells in slices of rat medial prefrontal cortex at low doses, but at higher dose an inhibition is observed (Liang and Wang,1998).

In recent years, a molecular mechanism has been suggested which may describe how sigma-1 receptor ligands increase the NMDA response. Calcium ions entering the cells through NMDA-receptor-related channels normally activate a potassium current via small-conductance calcium-activated K^+ channels (SK channels). This current shunts the NMDA receptor responses. Sigma-1 subtype-selective receptor agonists prevent SK channel opening, and consequently increase the NMDA receptor response (Martina, Turcotte, Halman and Bergeron,2007).

3. 6. Modulation of calcium homeostasis

In 2007, The sigma-1 receptor was identified as a new molecular chaperone targeting the ER sub domain associated with mitochondria [ie, the mitochondria- associated ER membrane (MAM)], regulating endoplasmic reticulum-mitochondrial inter cell survival and organellar Ca^{2+} signaling, and sensing endoplasmic reticulum Ca^{2+} concentration (Hayashi and Su,2007, Meunier and Hayashi,2010).

Also, Sigma-1 ligands have been reported to play a modulatory function in intracellular Ca^{2+} signaling; in other word, they modulate plasmalemmal voltage-dependent calcium channels. Interaction between sigma receptors and Ca^{2+} channels was proposed from investigates in which the increase in intracellular Ca^{2+} concentration mediated by depolarization was decreased by ligands in neuronal cultures or forebrain synaptosomes (Bermack and Debonnel,2005, Guitart, Codony and Monroy,2004, Monnet,2005). Nevertheless, in several of these experiments sigma-1 antagonists and sigma-1 agonists produced the same effects, which might be also due to the participation of sigma-2 receptors (Monnet,2005). Also, the selective sigma-1 agonists (+)-pentazocine and PRE 084 induced opposite effects on the escalation in Ca^{2+} concentration induced by depolarization with KCl in NG108 cells, but both effects were reverted by sigma-1 receptor antisense oligodeoxynucleotide (Hayashi, Maurice and Su,2000), proposing that they were both mediated by the cloned sigma-1 receptor. It consequently seems clear that more studies are required to clarify the function of these receptors in plasmalemmal voltage-dependent calcium channels.

The intracellular localization of sigma-1 receptors (mainly in endoplasmatic reticulum, but also in nuclear and plasma membranes and on mitochondria (Itzhak, Stein, Zhang, Kassim and Cristante,1991, Jiang, Mysona, Dun, Gnana-Prakasam, Pabla, Li, Dong, Ganapathy and Smith,2006, Mccann and Su,1990, Phan, et al.,2003)) proposes that these binding sites could be involved in the regulation of calcium mobilization.

Actually, sigma-1 receptor activation has been shown to affect calcium homeostasis. Studies of Ela et al. shown that Sigma-1 receptor agonists modulate contractility, calcium influx and beating rate in cultured cardiac myocytes (Ela, Barg, Vogel, Hasin and Eilam,1994). Intracellular levels of inositol triphosphate in these cells were increased as well (Novakova, Ela, Bowen, Hasin and Eilam,1998). In neuroblastoma–glioma (NG108) cells, various sigma-1 receptor agonists enhanced the bradykinin-induced increases in cytosolic free calcium with bell shaped dose response curves whereas this effect could be blocked by a sigma-1 receptor antisense oligonucleotide, suggesting that sigma-1 receptor activation facilitates IP3-receptor-mediated Ca^{2+} signaling(Hayashi, Maurice and Su,2000). In SH-SY5Y (neurob-lastoma) cells, the sigma-1 receptor agonist progesterone, (+)-pentazocine, pregnenolone, and DHEA competed for [^{3}H] also potentiated the bradykinin-induced Ca^{2+} response, and this potentiation was blocked by the sigma receptor antagonists haloperidol and progesterone(Hong, et al.,2004). By expression of either complete sigma-1 receptors or the N- or C-terminal segment of the sigma-1 receptor protein in MCF-7 breast cancer cells (which normally express few sigma-1 receptors), proof was obtained that sigma-1 receptor over expression results in an enhancement of bradykinin-, vasopressin- or ATP-induced calcium release, and that the C-terminal

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segment of the sigma-1 receptor is involved in the interaction with the inositol triphosphate receptor–ankyrin-B 220 complex [159].

Experiments in isolated adult guinea pig preparations have shown that sigma-1 receptor activation leads to activation of phospholipase C and the beta-1 and beta-2 isoforms of protein kinase C (Morin-Surun, et al.,1999). In isolated rat hippocampal neurons, receptor activation leads to a potentiation of NMDA-receptor-mediated increases of free intracellular calcium (Monnet, Morin-Surun, Leger and Combettes,2003). Nevertheless, in rat frontal cortical neurons, sigma receptor ligands were found to reduce the NMDA-induced Ca^{2+} influx. Sigma-1-subtype-selective compounds (igmesine, (+)-pentazocine) particularly affected the sustained phase of the Ca^{2+} response to NMDA, whereas non-subtype-selective compounds (DTG, haloperidol) reduced the initial and sustained phases to the same degree. The inhibition of the sustained phase was directly related to the affinity of the ligands to sigma-1 receptors. Thus, in frontal cortical neurons, sigma-1 receptors appear to facilitate the desensitization of the Ca^{2+} response to NMDA (Hayashi, et al.,1995). Attenuation of NMDA-induced calcium responses by sigma ligands in frontal cortical neurons was also observed in a later study, and that study confirmed that sigma ligands shifted the NMDA response from a sustained to a biphasic or transient event.

In an interesting study on the sigma-1 receptor agonist igmesine, the effect of intracerebroventricularly administered modulators of calcium influx and mobilization was examined on the reduction of immobilization time caused by igmesine in the forced swimming test. Using chelators of extracellular and intra-cellular calcium, L- and N-type voltage-dependent calcium channel antagonists and agonists, evidence was obtained that the antidepressant effect of igmesine is dependent not only on rapid Ca^{2+} influx (like that of classical antidepressants), but also on intracellular Ca^{2+} mobilization (Urani, et al.,2002).

Antagonists of voltage dependent calcium channels such as nimodipine impair the cognitive performance of rodents in various learning tests. Such impairments could be attenuated by pre administration of the sigma1 receptor agonists PRE084, and this attenuation could be completely prevented by co-administration of the sigma1 receptor antagonist BMY14802. Thus, calcium fluxes are implied in memory processes and an impairment of calcium influx through voltage-dependent calcium channels can, at least partially, be overcome by administration of a sigma-1 receptor agonist (Maurice, et al.,1995). Potentiation or attenuation of calcium signaling via sigma-1 receptors (both Ca^{2+} entry at the plasma membrane level via channels and Ca^{2+} mobilization from intracellular stores) may explain why selective sigma1 receptor agonists can modulate a wide variety of neuronal responses, and be the key mechanism by which sigma-1 receptors affect learning and memory (Monnet,2005).

4. DISEASES

4. 1. Sigma receptor and diseases

In this review, we focus on application sigma receptors as a potential target for the expansion of a new class of antidepressant drugs. This review begins with a summary of proof implicating sigma receptors in the actions of antidepressant drugs. Then, it provides a conceptual framework for potential mechanism(s) of action of sigma-active antidepressant drugs and an account of recent studies supporting this conceptual framework.

While sigma receptors (σ) were discovered in 1982, the physiological and biochemical applications of sigma receptors have just begun to reveal (Su and Hayashi,2003). After 31 years than discovery of sigma (σ) receptors, Because of their involvement in practically all major central nervous system (CNS) diseases, studying of them remain widely studied (D Banister and Kassiou,2012). The implication of sigma-1 and sigma-2 in the pathophysiologies of multiple affective disorders, including

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schizophrenia, depression, and anxiety, as well as movement (Parkinson's disease) and dysfunctions of memory (Alzheimer's disease), has encouraged the development of progressively selective sigma ligands for the capable of becoming treatment of CNS disorders (D Banister and Kassiou,2012, Fishback, Robson, Xu and Matsumoto,2010). Actually, several clinical antipsychotics and antidepressants have confirmed activity at sigma receptors at therapeutically relevant concentrations (Bowen, et al.,1990, Narita, et al.,1996). Methamphetamine and cocaine also interact with sigma receptors at physiologically-relevant concentrations, and there is comprehensive proof that sigma receptors are involved in both the toxic and rewarding effects of these widely abused stimulants, making σ receptors a promising target for the treatment of substance abuse (Matsumoto,2009, Nguyen, et al.,2005).

Pharmacological and biochemical studies suggest that there are manifold subtypes of sigma receptors. The best of them characterized binding sites that divide sigma receptors in two pharmacologically and functionally distinct subtypes, so-called sigma-1(σ_1) and sigma-2 (σ_2). However all sigma receptors are non-phencyclidine, non-opioid receptors, but they have diversity in size, anatomical distribution and drug selectivity (Guitart, Codony and Monroy,2004, Quirion, Bowen, Itzhak, Junien, Musacchio, Rothman, Tsung-Ping, Tam and Taylor,1992). The σ_1 receptor is known as an integral membrane protein which does not resemble amino acid homology with any mammalian receptor proteins. However, sigma-1 receptor has homology with fungal sterol isomerase, though it lacks sterol isomerase enzymatic activity (Su and Hayashi,2003). Vilneret al..(Vilner, John and Bowen,1995) have displayed that both sigma receptor subtypes, sigma-1 and sigma-2, are overexpressed in many human tumors and tumor cell lines from various tissues such as breast cancer, prostate cancer, glioma, neuroblastoma, malignant melanoma, and non-small-cell lung carcinoma. The elevated levels of sigma-1 and sigma-2in many human tumors and cancer cell lines have led to a concentrated effort in the expansion of sigma receptor targeting anticancer agents and imaging tools (Chu, Hajipour, Ramachandran and Ruoho,2011).

Pharmacological studies have showed that the σ_1 receptor is capable to bind a widespread range of compounds, including the antidepressant drugs fluvoxamine and sertraline, antipsychotics (Campbell, et al.,1989), opiates (Su,1982, Tam,1983, Weber, et al.,1986), antihistamines, serotonergic compounds (Tam,1983), adrenergic receptor ligands (beta-adrenergic) (Tam,1983, Weber, Sonders, Quarum, Mclean, Pou and Keana,1986), phencyclidine-like compounds (Contreras, et al.,1988), the psychostimulants cocaine and methamphetamine and cocaine analogs (Kahoun and Ruoho,1992, Sharkey, et al.,1988), steroids (Leonard,2004, Monnet, et al.,1995), cholesterol (Palmer, Mahen, Schnell, Djamgoz and Aydar,2007) neuropeptides (Leonard,2004), and the anticonvulsant drug phenytoin allosterically (Nakade, et al.,2003), although interestingly no known natural specific ligands have been discovered. Also, sigma-1 receptor ligands have been suggested to be useful in several therapeutic fields such as depression and anxiety, amnesic and cognitive deficits, analgesia, schizophrenia, dementia, and against some effects of drugs of abuse (such as methamphetamine and cocaine) (Cobos, Entrena, Nieto, Cendan and Del Pozo,2008). Sigma-1 receptors are broadly distributed in the CNS and play an important role in pain control, such as the periaqueductal gray matter, the superficial layers of the spinal cord dorsal horn, the locus ceruleus and rostroventral medulla (Alonso, Phan, Guillemain, Saunier, Legrand, Anoal and Maurice,2000, Kitaichi, et al.,2000).

In Recent years, the σ_2 receptor has been recognized as being progesterone receptor membrane component 1 (PGRMC1) (Xu, et al.,2011).

4. 2. Sigma-1 receptor chaperones and diseases

Hayashi and Su represented that the sigma-1 receptor has been postulated to be a ligand-regulated molecular chaperone in the endoplasmic reticulum that regulates cellular redox, signal transduction, ER stress, synaptogenesis and cellular survival (Hayashi and Su,2007). Due to absence of complexity allows to apharmacophore for the sigma-1 receptor that has been proposed by Glennonto involve the

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majority of sigma-1 ligands, although at the expense of predictive helpfulness (Glennon,2005). Nevertheless, no such agreement model exists for sigma-2 binding, and selective sigma-2 ligands are far outnumbered by those with selectivity for sigma-1.Therefore, the use of comparatively subtype non-selective sigma ligands animal models of disease has often unnoticed the independent roles of sigma receptor subtypes in such models. Van Waarde and et al. suggest that sigma-1 receptor agonists are encouraging compounds for the treatment of cognitive dysfunction by studying data from preclinical in a large variety of animal models (Van Waarde, Ramakrishnan, Rybczynska, Elsinga, Ishiwata, Nijholt, Luiten and Dierckx,2011). The pharmacological study of small molecule sigma receptor ligands for imaging applications and potential clinical treatment has been a rising area of cancer research. For example, Spruceet al..(Spruce, Campbell, Mctavish, Cooper, Appleyard, O'neill, Howie, Samson, Watt and Murray,2004) have confirmed that the small molecule sigma-1 receptor ligands BD-1047, rimcazole, and BD-1063, inhibited tumor cell survival while SKF-10047 and pentazocine repressed these effects. In 2004, Wang et al. examined the sigma-1 receptor expression in human breast cancer and evaluated the activity of the sigma-1 receptor ligands in breast cancer cell lines. They described that the sigma-1 receptor was found to be expressed in most neoplastic breast epithelial cells and cell lines (Wang, et al.,2004). Also, the sigma receptor ligands progesterone and haloperidol were found to inhibit growth of some breast cancer cell lines in a dose dependent manner (Wang, Rouzier, Albarracin, Sahin, Wagner, Yang, Smith, Bernstam, Marcelo and Hortobagyi,2004). In another paper, Sigma-1 antagonists have been shown to initiate tumor selective and caspase-dependent apoptosis, which could be rescued by sigma1 agonists(Spruce, Campbell, Mctavish, Cooper, Appleyard, O'neill, Howie, Samson, Watt and Murray,2004).Luedtkeet al. (Luedtke, et al.,2012) based upon their results acclaimed that: Sigma-1 receptor compounds are neuroprotective for HT-22 hippocampal cells, Sigma-1 selective compounds were neuroprotective using a rodent model of stroke, Sigma-1 selective compounds represent a therapeutic strategy for treating stroke.

4. 3. Cocaine and diseases

Cocaine have several mechanisms might also be important, but it commonly thought to act as a dopamine reuptake inhibitor to generate its reinforcing effects 105. Cocaine is a short acting, CNS psychostimulant (a role in psychostimulant activities has been suggested for the sigma-1 receptor, established upon methamphetamine binding (Nguyen, Mccracken, Liu, Pouw and Matsumoto,2005)) that behavioral alterations in both experimental humans and animals and produces marked physiological. Extremely, cocaine increases blood pressure, heart rate, locomotion and stereotypy, decreases fatigue, increases arousal and produces a profound euphoria (Johanson and Fischman,1989). In several reviews, the relationship between cocaine action and the sigma receptors has been described, and ligands for the sigma-1 receptor will attenuate the locomotors response to cocaine and block the sensitization (24, 37, 38). Also, several of the excitatory properties of methamphetamine have been proposed to be due to connections with the sigma-1 receptor. Furthermore, Regulation of cocaine effects (Matsumoto, et al.,2001, Mccracken, Bowen, De Costa and Matsumoto,1999), inhibition of proliferative responses to mitogens (Paul, et al.,1994), neuroprotective effects (Lysko, Gagnon, Yue, Gu and Feuerstein,1992), and increase in extracellular acetylcholine levels(Matsuno, Matsunaga, Senda and Mita,1993), have also been ascribed to sigma-1 receptor.

Nguyen et al. (Nguyen, Mccracken, Liu, Pouw and Matsumoto,2005), by investigation receptor binding and pharmacological to characterize the interaction between methamphetamine and both sigma receptor subtypes, have been shown that methamphetamine, similar cocaine, also binds to sigma-1 receptors in the micro-molar range, and with a 22-fold higher attraction than for sigma-2 receptors, therefore it is not unanticipated that sigma-1 ligands modulate particular effects of this psychostimulant. In recently studies, found that the sigma-1 antagonists MS-377 (Takahashi, et al.,2000), BMY 10802 (Ujike, et al.,1992) and NE 100 (Okuyama and Nakazato,1996) modulated the acute motor special effects of methamphetamine only weakly, if at all. Nevertheless, more new studies showed that the selective sigma-1 antagonists BD 1047 and BD 1063, as well as sigma-1 antisense oligodeoxynucleotide, inhibited methamphetamine casuedlocomotor activity (Nguyen, Mccracken,

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Liu, Pouw and Matsumoto,2005). Brammer et al. have reported that like methamphetamine or cocaine, the compound 3,4-methylenedioxymethamphetamine (MDMA), which is structurally connected to methamphetamine, revealed preferentially affinity for sigma-1 receptors rather than for the sigma-2 subtype, and that BD1063 alone had no influence on locomotor activity, but dose-dependently decreased the locomotor stimulant effects of (+)-MDMA (Brammer, et al.,2006). Moreover, MS-377 and BMY 14802, two well-known sigma-1 antagonists, inhibited the behavioral sensitization casued by the repeated administration of methamphetamine (Akiyama, et al.,1994, Takahashi, Miwa and Horikomi,2000, Ujike, Kanzaki, Okumura, Akiyama and Otsuki,1992). In 2004, Stefanski et al. (Stefanski, et al.,2004), in their studies with repeated cocaine administration, thought that sigma-1 receptors might play a role in neuronal plasticity subsequently the repeated administration of methamphetamine. In recent years, Sigma-1 receptor levels were found to be unchanged in rats passively treated with this psychostimulant; nevertheless, in rats self-administered with methamphetamine, sigma-1 receptors were upregulated in the rat midbrain, an area involved in reward processes and learning, but not in the frontal cortex, cerebellum, striatum and hippocampus. These remarks under scored the role of sigma-1 receptors in neuronal plasticity subsequently the consumption of psychostimulants. By exploring of the function of sigma-1 receptors in the conduct of other drugs of abuse was found that the sigma-1 antagonist BD 1047 was operational against ethanol caused locomotor stimulation, taste aversion, conditioned place preference and some symptoms of the abstinence syndrome after chronic ethanol consumption (Maurice, et al.,2003, Meunier, et al.,2006). Furthermore, studies of Meunier et al. (Meunier, Ieni and Maurice,2006) shown that sigma-1 receptor expression was increased in the hippocampus of mice subsequently chronic ethanol consumption. Nevertheless, both the sigma-1 agonist JO-1784 and the antagonist BD 1047 shared particular ameliorating properties against the self-restraint syndrome subsequently chronic ethanol consumption. These observations propose a pharmacological target for alleviating ethanol addiction and abstinence syndrome after withdrawal, though more behavioral tests should be done. Remarkably, an association has been proposed between polymer phisms in the sigma-1 receptor gene and alcoholism, supporting the function of sigma-1 receptors in chronic ethanol consumption (Cobos, Entrena, Nieto, Cendan and Del Pozo,2008, Miyatake, et al.,2004).

4. 4. Involvement of sigma-1 receptors in neuronal differentiation and neuroplasticity

Eliprodil, a neuroprotective drug with a great affinity agonist action at sigma receptors, strongly promotes myelination in neuron oligodendrocytecocultures. These data propose that upregulation of sigma-1 receptors is an important prerequisite for neuronal differentiation, and that sigma-1 receptor agonists like eloprodil may be of therapeutic interest in demyelinating diseases such as multiple sclerosis.

5. BINDING AND SYNTHESIS

5. 1. Binding affinities and synthesis and in vitro evaluation ligands for high-affinity binding to sigma receptor

The sensible design of highly subtype-selective ligands is confused by absence of structural information regarding the sigma binding site, and the great heterogeneity of identified ligands1(Banister, et al.,2010, Hajipour, et al.,2004). The range of structural classes is avid binders to sigma-1 and sigma-2 receptor which has hampered the expansion of selective binding models (Chu, et al.,2010, Glennon,2005). Not only find selective sigma-1 and sigma-2 receptor ligands may help in the characterization and isolation of this receptor, but also could lead to the expansion of novel therapeutics, mainly in oncology for sigma-2 receptor (Crawford and Bowen,2002, Guo, et al.,2012, Mésangeau, et al.,2011, Ostenfeld, Fehrenbacher, Høyer-Hansen, Thomsen, Farkas and Jäättelä,2005).

5. 1. 1. Interaction of sigma receptor subtypes with cocaine

In 1988, Sharkey et al. reported the ability of cocaine to bind to sigma receptors, for the first time. Nevertheless, the physiological relevance of interaction between them continued controversial for

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many years. The reason for the polemic stopped from the fact that cocaine has micro molar affinity for sigma receptors, a discovery that has been proved by numerous other laboratories (Matsumoto, et al.,2001, Ramamoorthy, Ramamoorthy, Mahesh, Leibach and Ganapathy,1995, Ritz and George,1993). In spite of the proportionately low affinity of cocaine for sigma receptors, cocaine has been presented to attain micro molar concentrations in the body (Mittleman and Wetli,1984, Spiehler and Reed,1985), proposing that the interactions confirmed in the receptor binding investigations are physiologically relevant (Matsumoto, Liu, Lerner, Howard and Brackett,2003).

5. 1. 2. synthesis and in vitro evaluation ligands for high-affinity binding to sigma receptor

In our previous study, the binding properties of various cocaine derivatives to the guinea pig liver sigma-1 receptor were surveyed. The consequences from evaluating the affinity of several derivatives of cocaine which were replaced on the phenyl ring shown that a main factor of binding to the guinea pig sigma-1 receptor binding site may be the expansion of a dipole in the ring in which the π electron density of the phenyl ring is reduced. This suggests that an electron-rich source is existing in the sigma-1 receptor binding site, such as the π system of an aromatic ring or other electron rich side chains, which interact with the phenyl ring of cocaine (Chen, Hajipour, Sievert, Arbabian and Ruoho,2007).

Also, we evaluated the influence of the benzoyl moiety of cocaine in regard to sigma-1 receptor binding and used the approach of photo affinity labeling to recognize the cocaine binding site on the sigma-1 receptor. Photo affinity labeling techniques have been applied intensively to recognize the binding sites of the G-protein-linked effectors, G-proteins, monoamine transporters, β-adrenergic receptor, and the sigma receptor-1 (E Ruoho, et al.,2012, Kahoun and Ruoho,1992, Resek and Ruoho,1988, Sievert, et al.,2000, Sievert and Ruoho,1997, Vaillancourt, et al.,1990). Besides, our results support this idea that a dipole in the phenyl ring of cocaine consequences in high affinity binding to the sigma-1 receptor (Chen, Hajipour, Sievert, Arbabian and Ruoho,2007).

The cocaine analogue [^{125}I]IACoc is a highly affinity sigma-1 receptor photo affinity label that specially recognized the 26 kDa sigma-1 receptor in brain homogenates, PC12 cells, and membranes derived from several organs (Kahoun and Ruoho,1992, Wilke, Lupardus, Grandy, Rubinstein, Low and Jackson,1999). Kahoun and Ruoho (Kahoun and Ruoho,1992) in their studies, have synthesized [^{125}I]IACoc, a carrier-free radio iodinated cocaine photo affinity label, to probe cocaine-binding proteins. Photo affinity labeling with 0.5 nM [^{125}I]IACoc selectively labels a 26-kDa polypeptide with the pharmacology of a sigma receptor in membranes prepared from human placenta, rat brain, and rat liver. Whereas the binding of cocaine to sigma receptors has been proposed to mediate the psychotomimetic properties of cocaine, this continues to be confirmed. [^{125}I]IACoc is a strong and highly specific photo affinity label for the haloperidol sensitive sigma receptor and will be worthwhile for its molecular and biochemical characterization.

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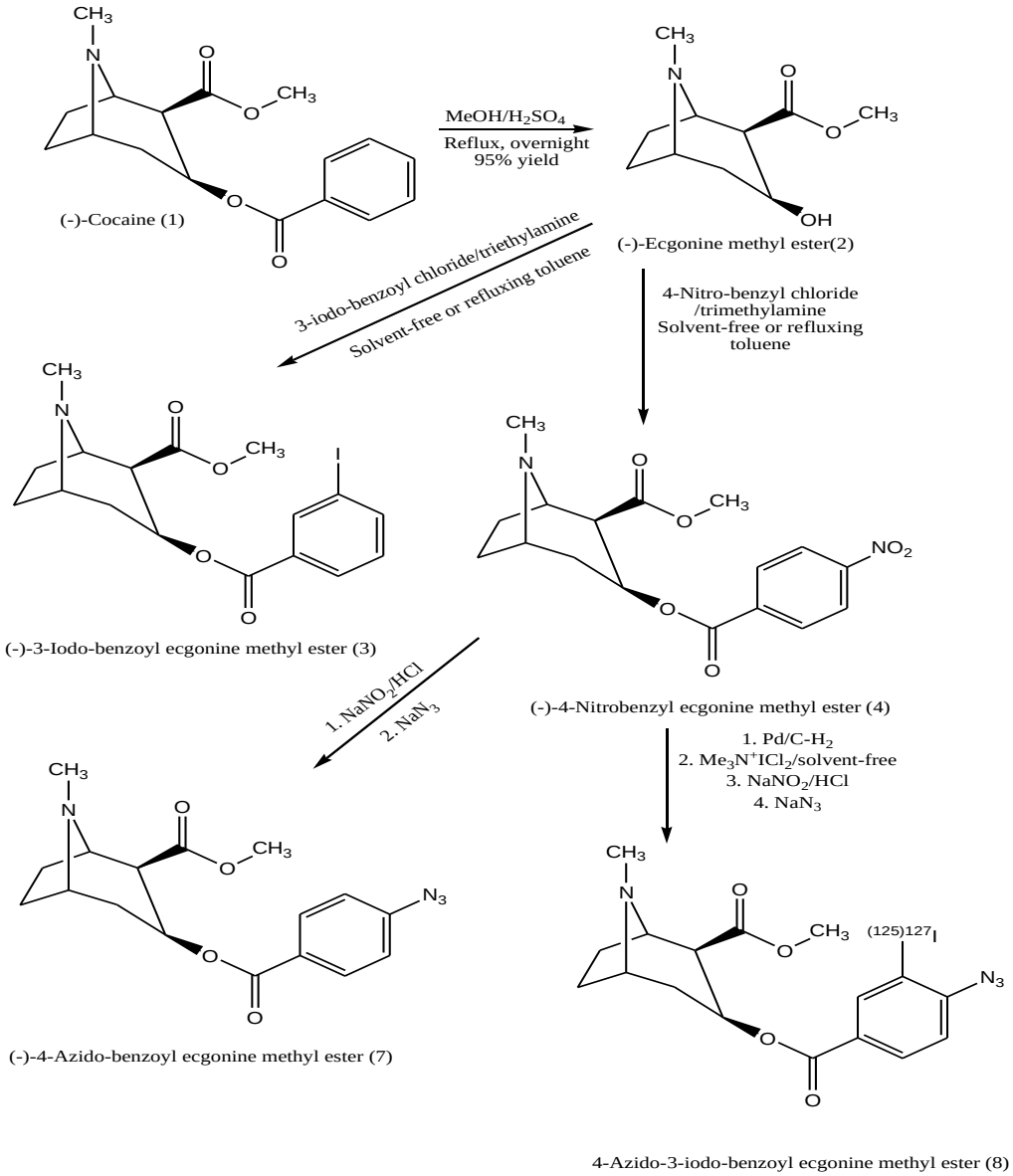

Synthesis of 3-Substituted Cocaine Derivatives

Scheme 1: Chemical Synthesis of the 3-substituted analogues

The synthesis scheme of the 3-substituted analogues (3-8) is shown in Scheme 1.

As another results of Kahoun and Ruoho (Kahoun and Ruoho,1992) studies, the cocaine photo affinity label [^{125} I]IACoc binds to the sigma-1 receptor with an affinity that is 2-3 orders of magnitude higher than the parent compound cocaine. Byuse of this photoprobe, we confirmed the act of setting in site for [^{125}I]IACoc to be Asp188 (Chen, Hajipour, Sievert, Arbabian and Ruoho,2007). In 2007, our laboratorial result show that the rank order of affinities are 4-amino-3-iodococaine < 3-iodococaine < 4-aminococaine < cocaine < 4-azidococaine < 4-nitrococaine < 4-azido-3-iodococaine (IACoc) (Chen, Hajipour, Sievert, Arbabian and Ruoho,2007).

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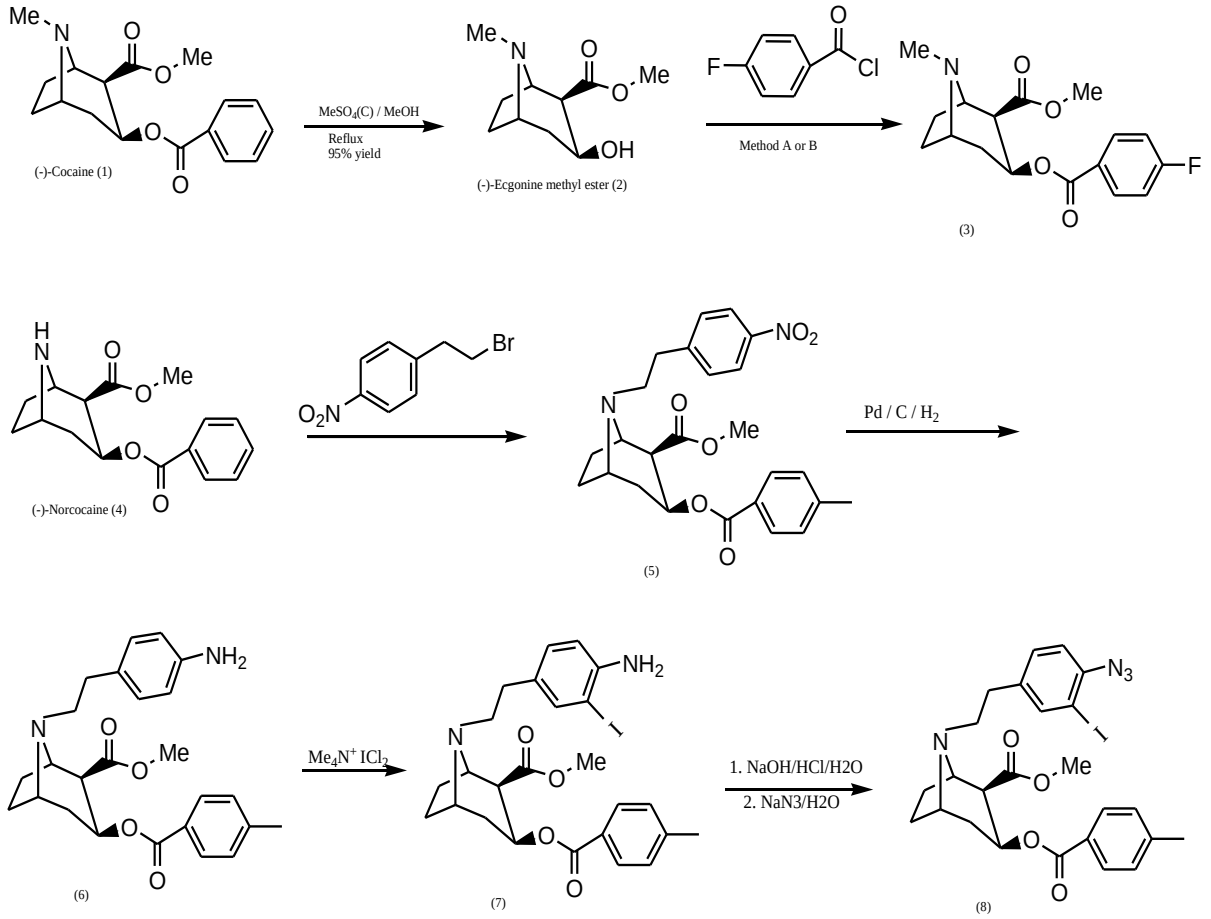
Results of kinetic analysis of (^{125}I)IACoc binding to rat liver microsomes shown two sites with Kd values of 19 and 126 µM, respectively. The existence or absence of proteolytic inhibitors throughout membrane preparation did not change the size of the photo labeled sigma receptor, representing that the 26-kDa polypeptide was not derived from a larger protein(Chen, Hajipour, Sievert, Arbabian and Ruoho,2007).

In 2008, we define two new positioned carrier-free, radiodinated photo affinity labels specially designed to probe the putative "nitrogen interacting region" of sigma-1 receptor ligands. These two photoprobes are [^{125}I]IAC44 and [^{125}I]-N-IACoc (Fontanilla, et al.,2008). In our laboratorial work, Since [^{125}I]IAC44 (Vagnerova, et al.,2006) and [^{125}I]-N-IACoc (Kekuda, Prasad, Fei, Leibach and Ganapathy,1996) both had an enough binding affinity for the sigma-1 receptor, these two photoprobes were synthesized as radioiodinated photo affinity labels and tested (Fontanilla, Hajipour, Pal, Chu, Arbabian and Ruoho,2008).



Scheme 2: Chemical Synthesis of N-Substituted Cocaine Derivatives

[^{125}I]-N-IACoc and Derivatives

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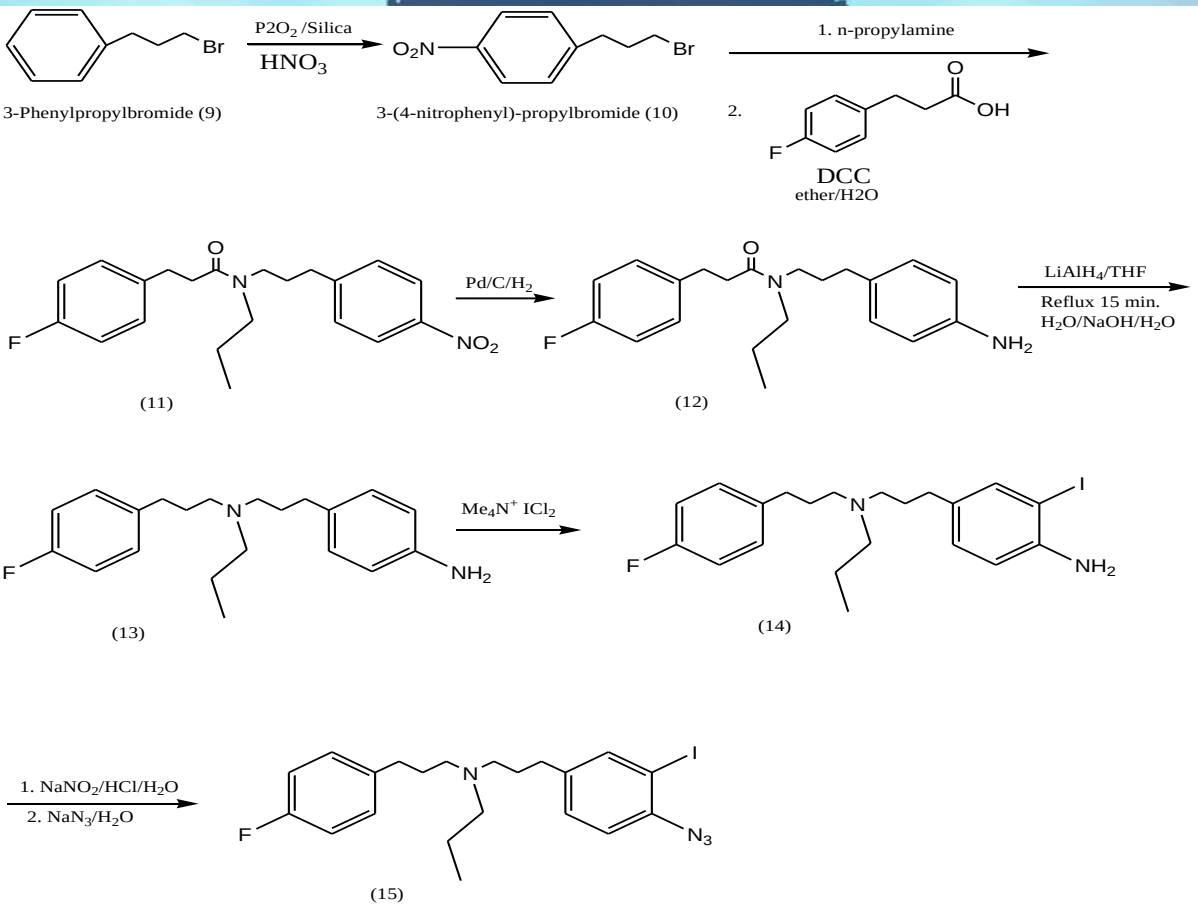
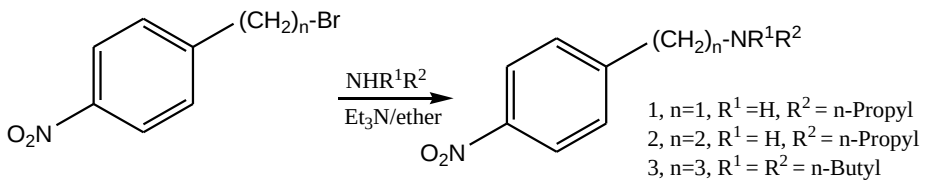


3-Phenylpropylbromide (9) 3-(4-nitrophenyl)-propylbromide (10) (11) (12) (13) (14) (15)

Scheme 3: Chemical Synthesis of N-Alkyl-N′-aralkyl Derivatives

[^{125}I]IAC44 and Derivatives

In previous work, we report the design, synthesis, and assessing of the relative affinities of a number of N-alkyl-N-aralkylor N,N-dialkyl compounds to the sigma-1 receptor in guinea pig liver membranes and in cytotoxicity assays (for their capability to inhibit the growth of numerous tumor cell lines)by competition assays against (+)-[^{3}H]-pentazocine and to the sigma-2 receptor in rat liver membranes, using [^{3}H]-ditolyl guanidine ([^{3}H]-DTG)(Hajipour, Fontanilla, Chu, Arbabian and Ruoho,2010). In this work, high affinity sigma-1 receptor compounds such as N-propyl-N0 -4-aminophenyl-ethyl-3-(4-nitrophenyl)propylamine (Ki=6 nM),N,N-dibutyl-3-(4-nitrophenyl)propylamine (Ki=0.36 nM), and N,N-dibutyl-3-(4-fluoro-phenyl)propylamine (Ki=17.7 nM) were introduced.



Scheme 1.

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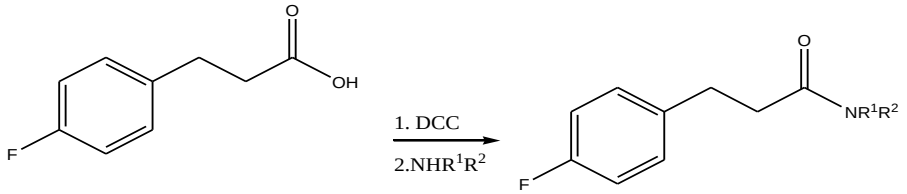
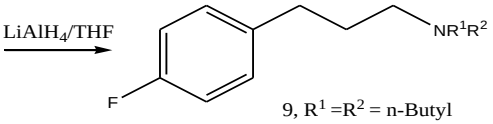
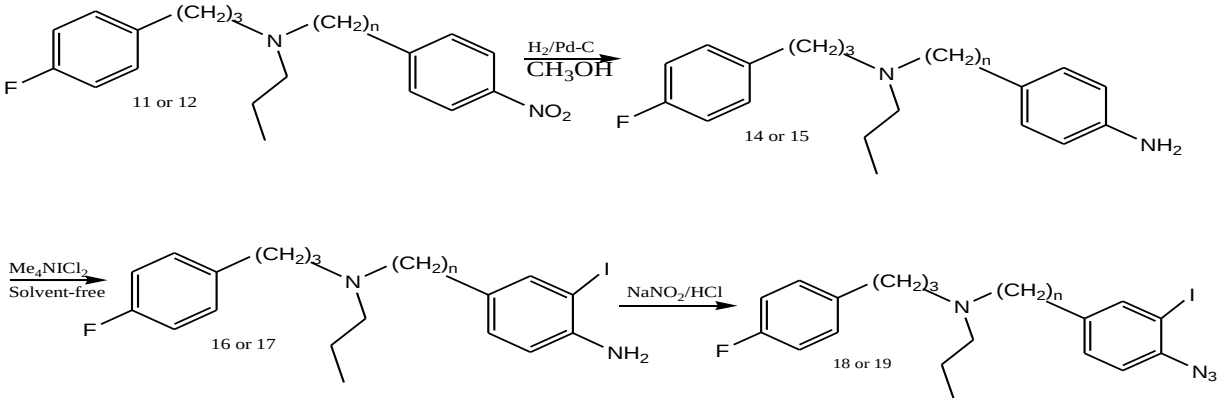


4, $R^1 = R^2$ = n-Butyl
5, $R^1 = R^2$ = n-Octyl
6, R^1 = n-Propyl, R^2 = (4-nitrophenyl)methyl
7, R^1 = n-Propyl, R^2 = (4-nitrophenyl)ethyle
8, R^1 =H, R^2 = n-Propyl

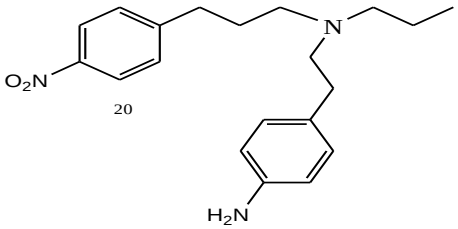


9, $R^1 = R^2$ = n-Butyl
10, $R^1 = R^2$ = n-Octyl
11, R^1 = n-Propyl, R^2 = (4-nitrophenyl)methyl
12, R^1 = n-Propyl, R^2 = (4-nitrophenyl)ethyle
13, R^1 =H, R^2 = n-Propyl

Scheme 2.



11,14,16,18, n = 1, 12,15,17,19, n = 2



Scheme 3.

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Formerly, we observed that these drugs have a mutual pharmacophore, which can also be generated from the chemical structure of fenpropimorph (Fontanilla, Johannessen, Hajipour, Cozzi, Jackson and Ruoho,2009). This chemical backbone iscomposed of a phenyl ring attached to a disubstituted nitrogen atom by an alkyl chain. Additional examination led to the observation that similar chemical backbones could be derived from other high affinity sigma-1 ligands such as cocaine and haloperidol (Fontanilla, Johannessen, Hajipour, Cozzi, Jackson and Ruoho,2009), resulting in a common N-alkyl-N-aralkyl or N,N-dialkylproduct. Several other sigma-1 ligands described in the paper support this structural pharmacophore such as 1-[2-(3,4-dichlorophenyl)ethyl-4-methylpiperazine (BD1063) (Matsumoto, et al.,1995), N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino)ethylamine (BD1047) (Matsumoto, Bowen, Tom, Vo, Truong and De Costa,1995), (piperazin-2-yl)methanol derivatives (Bedürftig and Wünsch,2004), metham-phetamine (Nguyen, Mccracken, Liu, Pouw and Matsumoto,2005), FN/C-1 to FN/C-4 (Barbieri, et al.,2003), (R/S)-4-(dimethylamino)-2-(napthalen-2-yl)butan-2-ol(Collina, et al.,2007), dimemorfan (Shin, et al.,2005), 1-methoxy-carbonyl-1-phenyl-2-cyclopropylmethylamines (Prezzavento, et al.,2007), 1-aralkyl-4-benzylpiperazine derivatives (Costantino, et al.,2005) and [^{11}C]SA4503 (Kawamura, et al.,2000).

In 2011, the observation that D-erythro-sphingosine binds to the sigma-1 receptor with comparatively high affinity (Ramachandran, Chu, Mavlyutov, Pal, Pyne and Ruoho,2009) provoked us to investigate monochainsphingosine like N-alkylamine molecules to recognize the relationship between the number of alkyl carbons on the molecule and sigma-1 receptor affinity. In this work, we done competitive displacement of [^{3}H]-(+)-pentazocine binding to the guinea pig sigma-1 receptor (Ramachandran, et al.,2007) and recognize that affinities of N-alkylamines for the sigma-1 receptor improved in the series. Our data indicate a positive correlation between the number of carbons and sigma-1 receptor affinity from butylamine to dodecylamine (Chu, Hajipour, Ramachandran and Ruoho,2011). These systematic binding investigations of binding of N-alkylamines to the pure sigma-1 receptor and N-alkylamine derivatives to both subtypes of sigma receptor have expanded our knowledge of properties of both sigma binding sites that may have been neglected since the find that tridemorph binds with high affinity to the sigma-1 receptor.

In this work, according to the test of a series of N-alkylamines for their affinity for the sigma-1 receptor, we discern a dependence on hydrocarbon chain length, whereby dodecylamine showed maximal binding. Previous investigations based on structure activity relations of identified sigma-1 receptor ligands shown that there is anobligation for at least one arylalkyl substitution on a nitrogen atom for high affinity for the sigma-1 receptor (Fontanilla, Johannessen, Hajipour, Cozzi, Jackson and Ruoho,2009, Gilligan, et al.,1994, Glennon,2005, Laggner, et al.,2005, Zampieri, et al.,2009).

Ablordeppey et al. (Ablordeppey, et al.,2000) shown that the existence of a nitrogen has is a significant pharmacophoric element for sigma-1 receptor binding. Besides, we previously showed that to enhance the affinity of sigma-1 receptor ligands N-3-(4-nitrophenyl)propyl and N-3-phenylpropyl substitution on the perform nitrogen of sigma-1 receptor ligands (Fontanilla, Hajipour, Pal, Chu, Arbabian and Ruoho,2008).

Structure activity investigations of sigma-1 receptor ligands have mostly focused on N,N dialkylphenylpropylamine molecules (Fontanilla, Johannessen, Hajipour, Cozzi, Jackson and Ruoho,2009) and N,N diarylalkylamine (Glennon,2005) but in common have over looked long chain N-alkylamines such as N,Ndimethylsphingosines (Ramachandran, Chu, Mavlyutov, Pal, Pyne and Ruoho,2009), D erythrosphingosine (Ramachandran, Chu, Mavlyutov, Pal, Pyne and Ruoho,2009), tridemorph (Moebius, Reiter, Hanner and Glossmann,1997), and glycosphingo lipids such as lactosylceramideand galactosylceramide (John, et al.,1995) that also bind to the sigma-1 receptor.

In previous work (Chu, Hajipour, Ramachandran and Ruoho,2011), we studied a number of N-alkylamines of changing chain lengths as sigma receptor ligands. Though the KI values for N-alkylamines were determined to be in the micro molar range, while N-3-(4-nitrophenyl)propyl and N-

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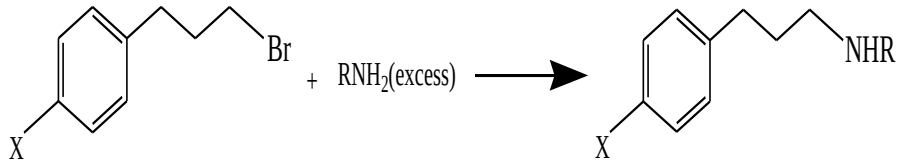
3-phenylpropyl derivatives of heptylamine, butylamine, octadecylamine, and dodecylamine were assessed as sigma receptor ligands, we determined that these compounds showed nanomolar affinities with both sigma receptor subtypes. A screen of highly affinity ligands heptylamine, and dodecylamine against a diversity of other receptors and/or transporters confirmed N-3-(4-nitrophenyl)propyl and N-3-phenylpropyl to be highly selective mixed both subtypes of sigma receptors ligands.



1a)X=H , R=nButyl
1b)X=NO_2, R= nButyl
2a)X=H, R=nHeptyl
2b)X= NO_2, R=nHeptyl
3a)X=H, R=nDodecyl
3a)X= NO_2, R=nDodecyl
4a)X=H, R=nOctadecyl
4b)X= NO_2, R=nOctadecyl

Whether N-alkylamine derivatives in our previous investigations inhibit cancer cell development via the activation of caspases remains undistinguishable sincerimcazole, exposed earlier to enhance the activity of caspases 3 and 7 (Spruce, Campbell, Mctavish, Cooper, Appleyard, O'neill, Howie, Samson, Watt and Murray,2004), did not show a positive caspase signal in our investigations (Chu, Hajipour, Ramachandran and Ruoho,2011). Ramachandran et al. (Ramachandran, Chu, Mavlyutov, Pal, Pyne and Ruoho,2009) presented that sphinganine, N,Ndimethylsphingosine, and sphingosine have weak interaction with the sigma-2 receptor; so, it was somewhat unpredicted that N-alkylamine derivatives bind to the sigma-2 receptor with KI values comparable to those attained for the sigma-1 receptor in GPLM. These data reveal a continuing challenge in the field to design selective sigma-2 receptor ligands. Additional investigations are required to recognize the binding region of the alkyl chain moiety of these molecules to advance our knowledge of the essential structural properties of sigma-2 receptors(Chu, Hajipour, Ramachandran and Ruoho,2011). In this study (Chu, Hajipour, Ramachandran and Ruoho,2011), of more importance is the discovery that N-alkylamine derivatives, including dodecylamine, heptylamineare high-selective for both sigma receptor subtypes. So, N-alkylamine derivatives may be appreciated tools for the functional and biochemical investigations of the sigma-1 and sigma-2 receptors and may demonstrate useful as potential diagnostic and/or anticancer therapeutic agents. Multiplex cytotoxicity assays show that heptylamine and dodecylamine inhibited growth of several cancer cell lines such asprostate, lung, colorectal, ovarian, breast, and central nervous system (Chu, Hajipour, Ramachandran and Ruoho,2011).
In 2013, we represent data demonstrating the photoincorporation of N-[3-(4-nitrophenyl)propyl]-N-dodecylamine (4-NPPC12), as one of these N-alkylamine derivatives, to the sigma-1 receptor (Chu, Ramachandran, Hajipour and Ruoho,2013).

5. 1. 3. High affinity sigma-2 receptor ligands as tools for the development of PET radiotracers

Regardless of ambiguities with sigma-2 receptor, for example existing disagreement between results of affinity chromatography technique with findings from fluorescence microscopy, the development of several high-affinity ligands (Berardi, et al.,2009, Tu, et al.,2007) is improving the knowledge of sigma-2 receptor, and attentiveness is on the increase since sigma-2 receptors are overexpressed in a widespread range of human tumor cell lines (Van Waarde, et al.,2010). Sigma-2 receptors characterize

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endogenous biomarkers for the diagnosis of tumors with noninvasive approaches such as Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET) (Van Waarde, A Rybczynska, K Ramakrishnan, Ishiwata, H Elsinga and Ajo Dierckx,2010). Also, sigma-2 receptor concentration and the proliferative status of tumors shown to be highly related to a number of cell lines (e.g.sigma-2 receptors concentration is about 10-fold higher in proliferative than quiescent cells), so as to sigma-2 receptor radiotracers may help for the imaging of the proliferative status of tumors serving to select the tumor treatment (Mach and Wheeler,2009).

The pharmacological investigation on sigma receptor ligands has an significant role in the cancer study for imaging diagnosis applications and potential clinical treatment whereby PET and SPECT techniques (Hashimoto and Ishiwata,2006, Van Waarde, A Rybczynska, K Ramakrishnan, Ishiwata, H Elsinga and Ajo Dierckx,2010). More recently, Xu et al. (Xu, Zeng, Chu, Pan, Rothfuss, Zhang, Tu, Zhou, Zeng and Vangveravong,2011) suggested that the hitherto unidentified identity of the sigma-2 binding site may be progesterone receptor membrane component 1 (PGRMC1), or a protein complex thereof.

5. 1. 4. Evaluation selective sigma-1 and sigma-2 receptor radioligand tomography

Radio iodinated photoactivatable photoprobes can give appreciated understandings regarding protein structure. For instance, Mach et al. (Mach, et al.,2001) in their studies compared the nonselective high-affinity radioligand 5-[^{125}I]iodo-2′-deox-yuridine ([^{125}I]IUdR) with 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) and N-[1-(4′-[^{18}F]fluorobenzyl)piperidin-4-yl]-3-bromophenylacetamide ([^{18}F]FBPBPA)in a tumor imaging investigation of nude mice with tumors grown from mouse mammary adenocarcinoma cell line 66. They acknowledged receptor-specific approval of the tracer(~25%) in the tumor and in the brain (~60%) with the following order of tumor uptake: [^{125}I]IUdR < [^{18}F]FBPBPA < [^{18}F]FDG (Mach, Huang, Buchheimer, Kuhner, Wu, Morton, Wang, Ehrenkaufer, Wallen and Wheeler,2001). Furthermore, the tumor:blood and tumor:muscle ratios were less for both [^{125}I]IUdR and [^{18}F]FDG than for [^{18}F]FBPBPA. These investigations confirmed the usefulness for sigma-1 receptor imaging agents as tools for anticancer therapy. A number of recent reviews are focused on the advance and use of sigma receptor ligands for these goals (Megalizzi, et al.,2012, Van Waarde, A Rybczynska, K Ramakrishnan, Ishiwata, H Elsinga and Ajo Dierckx,2010).

5. 1. 5. Synthesis and evaluation selective sigma-2 receptor

Mach and coworkers (Mach and Wheeler,2009) had extensive effort to create sigma-2 receptor ligands with enhanced selectivity and affinity, some of which have been advanced into imaging agents for proliferating tumor detection, in addition for cellular and tissue distribution of sigma-2 receptor. A main barrier for finding of sigma-2 selective ligands is the lack of knowledge of the molecular determinants for ligand/sigma-2 interactions (Hajipour, Guo, Pal, Mavlyutov and Ruoho,2011). Expansion of sigma-2 specific ligands, nevertheless, has been hindered by lack of knowledge of molecular determinants that underlie selective ligand-sigma-2 interactions.

In our previous study, We have discovered influence of electron donating and electron-withdrawing groups on ligand selectivity for the sigma-2 versus sigma-1 receptor using novel benzamideisoquinoline derivatives(Hajipour, Guo, Pal, Mavlyutov and Ruoho,2011). The electron-donating methoxy group amplified, while the electron with drawing nitro group reduced sigma-2 affinity. Particularly, adding an extra methoxy group (electron-donating) to the para-position (5e) of the benzamide phenyl ring of 5fdramatically improved (631 fold) the sigma-2 selectivity relative to the sigma-1 receptor (Hajipour, Guo, Pal, Mavlyutov and Ruoho,2011). This para-position appeared to be high-sensitive site for effective molecular manipulation of the sigma receptor selectivity using either the methoxy or nitro substituent. This investigation provides a valuable guide for further improving the sigma-2-over-sigma-1 selectivity of novel ligands (Hajipour, Guo, Pal, Mavlyutov and Ruoho,2011). We have earlier revealed that the electron-withdrawing nitro group importantly

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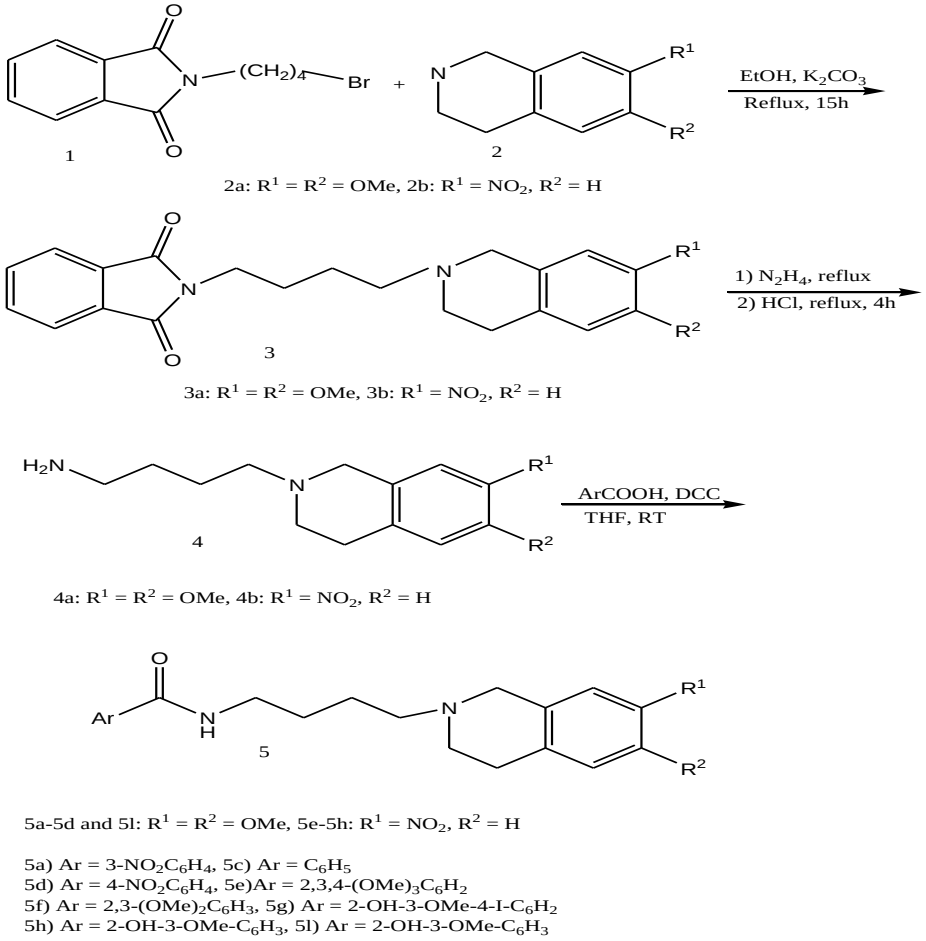
enhanced ligand affinity for the sigma-1 receptor (Chen, Hajipour, Sievert, Arbabian and Ruoho,2007, Hajipour, Fontanilla, Chu, Arbabian and Ruoho,2010).



2a: $R^1 = R^2 = OMe$, 2b: $R^1 = NO_2$, $R^2 = H$

3a: $R^1 = R^2 = OMe$, 3b: $R^1 = NO_2$, $R^2 = H$

4a: $R^1 = R^2 = OMe$, 4b: $R^1 = NO_2$, $R^2 = H$

5a-5d and 5l: $R^1 = R^2 = OMe$, 5e-5h: $R^1 = NO_2$, $R^2 = H$

5a) Ar = 3-$NO_2C_6H_4$, 5c) Ar = C_6H_5
5d) Ar = 4-$NO_2C_6H_4$, 5e)Ar = 2,3,4-$(OMe)_3C_6H_2$
5f) Ar = 2,3-$(OMe)_2C_6H_3$, 5g) Ar = 2-OH-3-OMe-4-I-C_6H_2
5h) Ar = 2-OH-3-OMe-C_6H_3, 5l) Ar = 2-OH-3-OMe-C_6H_3

Our data show that in a class of novel benzamide-isoquinoline derivatives, the electron-donating methoxy group preferred sigma-2 affinity but not sigma-1 binding, therefore improving sigma-2 selectivity (Hajipour, Guo, Pal, Mavlyutov and Ruoho,2011).

5. 2. Site binding sigma receptor

Results of hydrophobicity analysis show that the fungal sterol isomerases and receptor are not topologically dissimilar, each having three hydrophobic regions (Chen, Hajipour, Sievert, Arbabian and Ruoho,2007). One suggested model proposes that the first hydrophobic segment is likely to be a transmembrane domain (TMD) (Hanner, Moebius, Flandorfer, Knaus, Striessnig, Kempner and Glossmann,1996, Pal, Hajipour, Fontanilla, Ramachandran, Chu, Mavlyutov and Ruoho,2007), and the other two hydrophobic segments (highly conserved regions), are suggested as the steroid binding domain-like (SBDL I and SBDL II) regions due to high sequence homology with the steroid binding domain of the ERG2(Chen, Hajipour, Sievert, Arbabian and Ruoho,2007). However, the sigma receptor does not have sterol isomerase activity itself, nor can it release sterol isomerase-deficient yeast (Moebius, Striessnig and Glossmann,1997).

In 2002, Aydar et al. (Aydar, Palmer, Klyachko and Jackson,2002) proposed the model that the sigma-1 receptor contains two TMDs with the orientation of both the C and N termini on the same side of the membrane bilayer. Also in 2007, Hayashi et al. (Hayashi and Su,2007) suggested a model that

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contains both the C and N termini with an opposite orientation to model suggested by Aydar et al. (Aydar, Palmer, Klyachko and Jackson,2002) but at the same side of the membrane bilayer.

5. 3. Characterization binding site on the sigma-1 receptor and probing the steroid binding domain-like I and II (SBDLI and SBDLII)

Chemical cleavage and purification of the resulting labeled peptides was used to identifying the precise (^{125}I)Iodoazidococaine, derivatization site in the guinea pig sigma-1 receptor (Chen, Hajipour, Sievert, Arbabian and Ruoho,2007). Ramachandra net al. (Ramachandran, Lu, Prabhu and Ruoho,2007) have developed a pattern for the purification of the guinea pig sigma-1 receptor and more recently, in our laboratorial studies (Chen, Hajipour, Sievert, Arbabian and Ruoho,2007, Pal, Hajipour, Fontanilla, Ramachandran, Chu, Mavlyutov and Ruoho,2007) using radio labeled photo reactive ligands in separate investigations displayed that ligand binding sites on the sigma-1 receptors contain regions of the receptor that have been recognized as the SBDLI (amino acids 91–109) and the SBDLII (amino acids 176–194) in the yeast sterol isomerase.

In 2008, we define two new strategically positioned carrier free, radioiodinated photo affinity labels specially designed to probe the putative “nitrogen interacting region” of sigma-1 receptor ligands (Fontanilla, Hajipour, Pal, Chu, Arbabian and Ruoho,2008). By helping of probing the “nitrogen interacting region” of sigma-1 receptor ligands, we have synthesized two new strategically positioned carrier free, radioiodinated photo affinity labels, N-propyl-N-(4-azido-3-[^{125}I]iodophenylethyl)-3-(4-fluorophenyl)propylamine ([^{125}I]IAC44) and (-)-methyl 3-(benzoyloxy)-8-2-(4-azido-3-[^{125}I]iodobenzene)-1-ethyl-8-azabicyclo[3.2.1]octane-2-carboxylate ([^{125}I]-N-IACoc), by strategic placement of the radioactive iodine and a photoactivatable aryl azideon the nitrogen. Following specific binding site covalent derivatization and subsequent Endo Lys C and CNBr digestions to cleave the photo labeled pure protein, the sigma-1 receptor binding site peptides specifically derivatized by [^{125}I]-N-IACoc and [^{125}I]IAC44 were identified.

Another photoprobe based on the sigma ligands that bind to the sigma-1 receptor fenpropimorph, 1-N-(2-3-[^{125}I]iodophenyl)propane ([^{125}I]IAF), was found to label a peptide in both the SBDLII and SBDLI (Pal, Hajipour, Fontanilla, Ramachandran, Chu, Mavlyutov and Ruoho,2007). Supplementary investigations of the binding site(s) using the high affinity sigma-1 photoprobe 1-N-(2-3-[^{125}I]iodophenyl)propane ([^{125}I]IAF) presented specific derivatization of the SBDLI in addition to the SBDLII. This has led to the deduction that SBDLI and SBDLII comprise part, if not all, of the main sigma-1 receptor binding site (Pal, Hajipour, Fontanilla, Ramachandran, Chu, Mavlyutov and Ruoho,2007). In our investigation, photoprobe was presented to derivatize the single cysteine residues as mixed disulfides at position 94 in the SBDLI region of the wild type guinea pig-1 receptor (Cys94) and at position 190 in the SBDLII region of a mutant guinea pig-1 receptor (C94A,V190C), both in a ligand (haloperidol or (+)-pentazocine)-sensitive manner (Guo, et al.,2005). Meaningfully, photocross-linking followed by Endo Lys-C cleavage under reducing conditions and intramolecular radiolabel transfer from the SBDLII to the SBDLI region in the mutant receptor and, contrariwise, from the SBDLI to the SBDLII region in the wild type receptor was observed. Our results support a model in which the SBDLII and SBDLI regions are juxtaposed to form, at least in part, a ligand binding site of the sigma-1 receptor (Pal, et al.,2008).

We have been experienced in identifying the ligand-binding region of the sigma-1 receptor by photo probe (photo affinity labels) (Chen, Hajipour, Sievert, Arbabian and Ruoho,2007, Fontanilla, Hajipour, Pal, Chu, Arbabian and Ruoho,2008, Pal, Hajipour, Fontanilla, Ramachandran, Chu, Mavlyutov and Ruoho,2007). In our previously studies, we demonstrated that a high-affinity sigma-1 selective photo label [^{125}I]IACocphotolabeled Asp188 (aspartate 188)sited on SBDLII within the C-terminal third hydrophobic region of the sigma-1 receptor (Chen, Hajipour, Sievert, Arbabian and Ruoho,2007), [^{125}I]IAF photo labeled both SBDLII and SBDLI (Pal, Hajipour, Fontanilla, Ramachandran, Chu, Mavlyutov and Ruoho,2007), and a radio iodinated benzophenone bifunctional

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cross-linking reagent tethered together SBDLII and SBDLI indicating an approximate 8 Å distance between these two domains (Chen, Hajipour, Sievert, Arbabian and Ruoho,2007).

Moreover, C-terminal truncations of the last 15 amino acids from the C-terminal region of the sigma-1 receptor displayed reduced levels of [^{125}I]IACoc photo labeling (Chen, Hajipour, Sievert, Arbabian and Ruoho,2007). Several biochemical investigations from our laboratories in addition to others using site-directed mutagenesis have also confirmed the importance of the C-terminal half of the sigma-1 receptor for ligand binding (Chen, Hajipour, Sievert, Arbabian and Ruoho,2007, Fontanilla, Hajipour, Pal, Chu, Arbabian and Ruoho,2008, Seth, Ganapathy, Conway, Bridges, Smith, Casellas and Ganapathy,2001). In 1999, Ganapathy et al. (Ganapathy, et al.,1999) have revealed that a sigma-1 receptor splice variant in Jurkat human T lymphocyte cells lacking amino acids 119−149 had a reduced level of [^{3}H]haloperidol binding. Specially, substitutions of glutamate 172 and Asp126 with glycine completely abolished binding of [^{3}H] haloperidol to the sigma-1 receptor 31 in partial support for the idea that the C-terminus is important for ligand binding.

The binding site is collected of the SBDLII region (amino acids 176-194), which surrounds the phenyl ring also initiate in all sigma-1 receptor ligands. It is more probable that the first transmembrane segment additionally supports ligand binding via a close interaction with SBDLII and/or SBDLI. The communication of endogenous ligands and/or sigma-1 receptor ligands may be further controlled by cholesterol, which has been confirmed to bind to two amino acid segments, 161 to 180 and 191 to 210, which flank the SBDLII region (Palmer, Mahen, Schnell, Djamgoz and Aydar,2007). Binding to cholesterol in this C-terminal region was further confirmed to be reduced by the sigma-1 ligand, SKF-10047 (Palmer, Mahen, Schnell, Djamgoz and Aydar,2007). On the whole, the N-substituted photo probes described herein recognize an intramolecular juxtaposition of the TM1/SBDLI region of the sigma-1 receptor to the SBDLII region to create a ligand binding site (Fontanilla, Hajipour, Pal, Chu, Arbabian and Ruoho,2008).

5. 4. Evidence of receptor dimers; Photoaffinity labeling of the sigma-1 receptor with N-[3-(4-Nitrophenyl)propyl]-N-dodecylamine

In our previous works, we have studies on the binding of N-[3-(4-nitrophenyl)propyl]alkan-1-amines and N-(3-phenylpropyl) alkan-1-amines (PPC4, PPC7, PPC12, PPC18, 4-NPPC4, 4-NPPC7, 4-NPPC12, and 4-NPPC18) to the sigma-1 receptor (Chu, Hajipour, Ramachandran and Ruoho,2011, Chu, Ramachandran, Hajipour and Ruoho,2013). In 2013, we demonstrate the detection of photo-cross-linking by one of these molecules, 4-NPPC12, to the sigma-1 receptor. The unique photochemistry of 4-NPPC12 allowed its covalent photo incorporation into the sigma-1 receptor and resulted in an alteration of the electrophoretic migration pattern of the receptor on SDS gels (Chu, Ramachandran, Hajipour and Ruoho,2013). Our results on binding revealed that affinities improved linearly with carbon chain length and maximal binding was attained with 12 carbons. Furthermore, four of PPC7,4-NPPC7, PPC12, and 4-NPPC12 (N-alkylamine derivatives)displayed high selectivity for both subtypes of sigma receptors when evaluated in a binding screen of more than 40 other membrane receptor/transporter targets, and these N-alkylamine derivatives have confirmed promising anticancer activities against an array of cancer cell lines (Chu, Ramachandran, Hajipour and Ruoho,2013).

The consequential photo-cross-linking of 4-NPPC12 to the sigma-1 receptor resulted in arise in the electrophoretic mobility (by 3 kDa) of half of the population of the sigma-1 receptor molecules. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF-TOF) and tandem mass spectrometry recognized histidine 154 as the site of 4-NPPC12 covalent photoincorporation. Mechanistically, the earlier suggested “half-site” reactivity of binding of [^{3}H]-(+)-pentazocine to the pure sigma-1 receptor suggests that 4-NPPC12 may bind to a dimer of the receptor with a 2:1 receptor

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monomer: ligand ratio (Chu, Ramachandran, Hajipour and Ruoho,2013). light-dependent photo insertion of 4-NPPC12 resulted in an enhanced electrophoretic mobility of only 50% of the derivatized receptor molecules as assessed by sodium dodecyl sulfate–polyacrylamide gel electrophoresis. The suggested binding and reactivity of 4-NPPC12 evoke a ligand binding model for the sigma-1 receptor that likely involves a receptor dimer and/or oligomer (Chu, Ramachandran, Hajipour and Ruoho,2013).

However the physiological significance of the sigma-1 receptor dimer in the context of the cellular environment is unclear, a new report confirmed that mutation of glutamic acid 102 to glutamine (E102Q) in the sigma-1 receptor produced a detergent-resistant apparent homodimer as assessed by SDS–PAGE (Al-Saif, et al.,2011). 40 The sigma-1 receptor harboring an E102Q mutation was proposed by the authors to cause juvenile amyotrophic lateral sclerosis (JALS) in a consanguineous family with a high familial incidence of this neurodegenerative disease. Therefore, it will be important in the future to define the functional forms of the sigma-1 receptor in a cellular context and to define whether diverse classes of ligands (agonists vs. antagonists) vary in their futures in binding to different quaternary forms of the receptor (Chu, Ramachandran, Hajipour and Ruoho,2013).

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