

Sigma Receptors

Key References

- Ablordeppay, S.Y., et al., Is a nitrogen atom an important pharmacophoric element in sigma ligand binding?, *Bioorg. Med. Chem.*, **8**, 2105-2111 (2000).
- Abou-Gharbia, M., et al., Sigma receptors and their ligands: The sigma enigma., *Annu. Rep. Med. Chem.*, **28**, 1-10 (1993).
- Bowen, W.D., Sigma receptors: Recent advances and new clinical potentials., *Pharm. Acta. Helv.*, **74**, 211-218 (2000).
- Codony, G. and Monroy, X., Sigma Receptors: Biology and therapeutic potential. *Psychopharmacology*, **174**, 301-319 (2004).
- Debonnel, G. and de Montigny, C., Modulation of NMDA and dopaminergic neurotransmissions by sigma ligands: Possible implications for the treatment of psychiatric disorders., *Life Sci.*, **58**, 721-734 (1996).
- Ghelardini, C., et al., Pharmacological identification of SM-21, the novel σ_2 antagonist. *Pharmacol. Biochem. Behav.*, **67**, 659-662 (2000).
- Karbon, E.W. and Enna, S.J., Pharmacological characterization of sigma binding sites in guinea-pig brain membranes., *Adv. Exp. Med. Biol.*, **287**, 51-59 (1991).
- Matsumoto, R.R., et al., σ receptors: potential medications development target for anti-cocaine agents., *Eur. J. Pharmacol.*, **469**, 1-12 (2003).
- Matsumoto, R.R. and Pouw, B., Correlation between neuroleptic binding to sigma (1) and sigma (2) receptors and acute dystonic reactions., *Eur. J. Pharmacol.*, **401**, 155-160 (2000).
- Maurice, T. and Lockhart, B.P., Neuroprotective and anti-amnesic potentials of sigma (sigma) receptor ligands., *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **21**, 69-102 (1997).
- Quirion, R., et al., A proposal for the classification of sigma binding sites., *Trends Pharmacol. Sci.*, **13**, 85-86 (1992).
- Walker, J.M., et al., Sigma receptors: Biology and function., *Pharmacol. Rev.*, **42**, 355-402 (1990).

Overview

Although they have undergone a substantial transformation from the time they were first proposed in the mid-1970s, a unifying picture appears to be emerging for sigma receptors. Current interest is related to the possibility that sigma receptors may constitute favorable targets for drug design in conditions such as psychiatric and movement disorders, amnesia, depression, cancer, inflammation and cocaine addiction. To achieve this aim, it is necessary to characterize the binding sites pharmacologically and identify selective ligands.

It is now generally accepted that there are two sigma receptor subtypes, referred to as σ -1 and σ -2. However, despite evidence for the existence of "sigma binding substances", endogenous ligands have yet to be identified. Current knowledge regarding the molecular nature of the sigma receptors has improved in recent years. For example, using photo-affinity labeling, the σ -1 receptor was found to have a molecular weight of 25 kDa, while a value of 18-21 kDa was determined for the σ -2 receptor. The σ -1 receptor has also been cloned from guinea pig, rat, mouse and human tissue and shows a greater than 90% species homology. Although it possesses no enzymatic activity, the σ -1 receptor has a sequence similarity to the fungal $\Delta^{8,7}$ -isomerase enzyme. This, and perhaps the fact that steroids have moderate affinity at sigma receptors, has led to suggestions that they may play a role in neurosteroid biosynthesis. However, no homology exists between the σ -1 receptor and the mammalian $\Delta^{8,7}$ -isomerase enzyme.

Steroids display moderate to weak binding affinities at sigma receptors. Because there are no known endogenous ligands for the sigma receptors, the focus has remained on

steroids behaving as possible endogenous ligands for sigma receptors. Consistent with this idea is the fact that steroids may effect several physiological actions through sigma receptors. Yet there is evidence suggesting that sigma ligands may require a nitrogen atom, possibly in the protonated form, as a pharmacophore element, to achieve high affinity binding at the σ -1 receptor. Interestingly, steroids do not contain a nitrogen atom.

The σ -1 subtype is characterized by its high affinity and selectivity towards the (+)-stereoisomer of the benzomorphans and is found in high levels in guinea-pig brain. It has been shown to regulate central cholinergic function, negatively modulate agonist-stimulated phosphoinositide turnover, modulate dopamine release from dopaminergic neurons, modulate NMDA-type glutamate receptor electrophysiology, modulate opioid analgesia, inhibit amnesia, provide neuroprotection, and activate pyramidal neurons in the hippocampus of the rat through NMDA induction. Based on the later pharmacological property, several compounds are now classified as either putative receptor agonists, including (+)-pentazocine, L-687,384, BD 737, JO-1784 or putative antagonists, haloperidol, BMY 14802, DuP 734, NE-100, AC915, E5842 and MS-377. [³H]-Pentazocine is the primary selective radioligand for the determination of binding affinities at the σ -1 receptor. More recently, it has been confirmed that σ -1 selective ligands do attenuate cocaine-induced toxicity in animal models and they might play a role as anti-cocaine agents in man.

The picture is less clear with regard to the σ -2 sigma receptor primarily because of the lack of σ -2 selective agents. In contrast to

σ -1 sigma receptors, σ -2 receptors show a slight preference for the (–)-stereoisomers of the benzomorphans. Apart from the nervous system, high densities are found in liver and kidney and very high densities in tumor cell lines derived from various tissues, including gliomas, neuroblastomas, melanoma and carcinoma cell lines of breast, prostate and lung. Interestingly, σ -2 selective agonists have been shown to induce cell death in C6 glioma cell lines from both neuronal and non-neuronal origins. The mode of this cell death has been elucidated to be apoptotic in nature and modulation of intracellular calcium may play a role. Current evidence suggests that while σ -2 agonists may be useful as anticancer agents, σ -2 antagonists may find therapeutic utility in attenuating the motor side effects associated with typical antipsychotics. Alternatively, antipsychotic agents without sigma-binding affinity may serve as novel antipsychotics without the acute and long-term extrapyramidal side effects associated with current drugs.

DTG is a non-selective ligand for σ -1 and σ -2 receptors, but [³H]-DTG (in the presence of dextrallorphan to mask σ -1 sites) serves as an effective radioligand for determining binding affinity at σ -2 receptors. While these receptors have been implicated in cell proliferation and motor disturbances, the lack of selective ligands has hampered their full pharmacological characterization. Currently identified selective σ -2 ligands include CB 184, BIMU-8, CB 64D, ibogaine, ifenprodil, SM-21 and Lu28-179.

Sigma Receptors

| CURRENTLY ACCEPTED NAME | σ -1 | σ -2 |
|--------------------------------|---|---|
| ALTERNATE NAME | Sigma-1 | Sigma-2 |
| LIGANDS | (+)-Pentazocine (P127), ^a Rigmarole (346438), ^a L-687,384 (L8539), ^a BD 737 ^a , JO-1784, ^a DTG (207713), (+)SKF-10,047 (A114), Haloperidol (H1512) ^b , BMY 14802 ^b , R(+)-3-PPP (P102), ^b DuP 734, ^b NE-100, ^b AC915 (A3595), SA4503, ^a E5842, MS-377 | DTG (207713), Ifenprodil (I2892), Ibogaine (I7003), CB 184, CB 64D, SM-21, ^b BIMU-8, Lu28-179 |
| SIGNAL TRANSDUCTION MECHANISMS | Not known | Not known |
| RADIOLIGANDS OF CHOICE | [³ H]-(+)-Pentazocine | [³ H]-DTG |
| TISSUE EXPRESSION | Brain, heart | Liver, brain |
| PHYSIOLOGICAL FUNCTION | Poorly characterized | Not known |
| DISEASE RELEVANCE | Neuropsychiatric disorders, depression, amnesia, anti-cocaine | Cancer, motor disorders |

Abbreviations

AC915: 2-(1-Pyrrolidinyl)ethyl 3,4-dichlorophenylacetate oxalate
BD 737: 1S,2R-(+)-cis-N-[2-(3,4-Dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)cyclohexyl amine
BIMU-8: Endo-N-(8-Methyl-8-azabicyclo[3,2,1]oct-3-yl)-2,3-dihydro-(1-methyl)ethyl-2-oxo-1H-benzimidazole-1-carboxamide HCl
BMY 14802: a-(4-Fluorophenyl)-4-(5-fluoro-2-pyridinyl)-1-piperazinebutanol
CB 184: (+)-1R,5R-(E)-8-(3,4-Dichlorobenzylidene-5-(3-hydroxyphenyl))-2-methylmorpharn-7-one
CB 64D: (+)-1R,5R-(B)-8-Benzylidene-5-(3-hydroxyphenyl)-2-methylmorpharn-7-one
DTG: Di(2-tolyl)guanidine
DuP 734: 1-(Cyclopropylmethyl)-4-[2-(4"-fluorophenyl)oxoethyl]piperidine HBr
E5842: 4-[4-Fluorophenyl]-1,2,3,6-tetrahydro-1-[4-[1,2,4-triazol-1-yl]butyl]pyridine citrate
JO-1784: (+)-N-Cyclopropylmethyl-N-methyl-1,4-diphenyl-1-ethylbut-3-en-1-ylamine
L-687,384: 1-Benzylspiro(1,2,3,4-tetrahydronaphthalene-1,4-piperidine)
Lu28-179: 1'-[4-[1-(4-Fluorophenyl)-1-H-indol-3-yl]-1-butyl]spiro[iso-benzofuran-1(3H),4'-piperidine]
MS-377: (R)-(+)-1-(4-Chlorophenyl)-3-[4-(2-methoxyethyl)piperazin-1-yl]methyl-2-pyrrolidinone L-tartrate
NE-100: N,N-Dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine
3-PPP: 3-(3-Hydroxyphenyl)-N-(1-propyl)piperidine
SA4503: 1-(3,4-Dimethoxyphenethyl)-4-(phenylpropyl)piperazine
(+)-SKF-10,047: (+)-N-Allylnormetazocine hydrochloride
SM-21: 3- α -Tropanyl-2-(4-chlorophenoxy)butyrate

FOOTNOTES

- a** Putative σ receptor agonists.
b Putative σ receptor antagonists.