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Sigma 1 Receptor: Recent Focus of Modern Bio-Molecular Research in Neuropsychiatry

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ABSTRACT

Currently, the focus of bio-molecular research is centered on sigma receptors. Sigma receptors are initially believed to be the receptor for opioids; however clinical research has revealed that they are a group of non-opioid receptors with diverse biological functions. Ligands binding with sigma receptor exert their action through activation of multiple neurotransmitter systems. Sigma receptors are involved in various neuropsychiatric disorders like – depression, schizophrenia, anxiety disorders, substance use disorders, pain, dementia and numerous other physical illnesses.

KEYWORDS: Sigma receptor, Bio-molecular research, Neuropsychiatric disorders

Introduction

In psychiatric illnesses, there occurs disturbance in the neurotransmission. This strongly suggests the biological basis of psychiatric illnesses. Continuous research over decades has revealed that psychiatric illnesses like schizophrenia, mood disorders, substance use disorders, anxiety disorders, attention deficit hyperkinetic disorder, dementia, personality disorders are associated with disturbances in the neurotransmission of dopamine, serotonin, nor-epinephrine, GABA, glutamate, acetyl choline etc. In the last two decades the focus of bio-molecular and pharmacological research has been shifted from dopamine, serotonin and nor epinephrine receptors to the newer receptors like glutamate. In the last decade, much research has been conducted on sigma receptors and their role in different neuro-psychiatric disorders. Sigma receptors were initially believed to be the receptor for opioids; however the clinical research has revealed that – they are a group of non-opioid receptors with diverse biological functions [1].

The Sigma 1 receptor – Historical aspects

Martin et al (1976), in their study on the effects of morphine- and nalorphine- like drugs on dogs, suggested about a new subtype of opioid receptors that modulate psychotic manifestations induced by several opioid group of drugs and named it as sigma receptors [2]. Su TP (1982), worked on a protein receptor which has affinity for SKF-10047 and Pentazocine, which was later termed as "Sigma receptor" [3]. As the sigma receptor ligand SKF-10047 also binds with PCP sites and phencyclidine binds with sigma receptor, the status of sigma receptor was unclear; however subsequent research established that sigma receptors are different from PCP sites [4, 5].

Till date, two subtypes of sigma receptors have been identified, which are named as sigma-1 (σ1) & sigma -2 (σ2) receptors [1]. Hellewell and Bowen (1990) discovered these subtypes of sigma receptors [6].

The Sigma 1 Receptor – Pharmacologic aspects

After Northern blot analysis, it was found that sigma-1 receptors amply exist in the liver and reasonably in other areas like – kidney, lungs, brain, intestine, spleen, adrenal gland and placenta [1, 7]. In the human brain, the sigma 1 receptor is mainly distributed in areas like – cranial nerve nuclei, mesencephalon, red nucleus, periaqueductal gray matter, substantia niagra, hippocampus (dentate gyrus) para-ventricular and ventro-medial hypothalamic nuclei [1, 8]. Immune-histo-chemical studies have revealed that sigma 1 receptors are also located in the olfactory bulb, purkinje cells of cerebellum and basal ganglia (caudate nucleus and putamen) [1, 9]. Sigma 1 receptors are located at the endoplasmic reticulum of the cell and mediate action through multiple neurotransmitters [10]. Many drugs like – Antidepressants (Selective Serotonin Reuptake Inhibitors, Tricyclic Antidepressants), pro-cognitive agents (Memantine, Donepezil), Anesthetic agents (Ketamine), addictive substances (Cocaine, Phencyclidine, Pentazocine), antitussives (Dextromethorphan) have sigma 1 receptor agonistic activity [10, 11]. The antipsychotic haloperidol has antagonistic activity against the sigma 1 receptor [11]. Fluvoxamine is a potent sigma 1 receptor agonist and facilitates neurite outgrowth by augmenting the nerve-growth factor (NGF), hence having neuro-protective effect [10]. Sigma 1 receptor agonists – fluvoxamine and donepezil cause improvement in neuro-cognitive function in animal models of schizophrenia with phencyclidine induced cognitive impairment [10]. Other than fluvoxamine and donepezil, sigma 1 receptor agonists like neuro-steroids also improve cognitive impairments in various neuropsychiatric conditions [10]. Ligands of sigma 1 receptors modulate glutaminergic and serotonergic neurons and also facilitate NMDA receptor mediated dopamine release [12, 13].

Recent research on role of sigma receptors in neuropsychiatry

Most of the research data available on sigma receptors are limited to animal studies, molecular research and review articles or literature research with very few clinical and randomised control trials. The recent research on the role of sigma receptors on neuropsychiatry is highlighted.

1. Sigma receptors as an evolving drug target in neuropsychiatric illnesses: After the extensive study of the various actions of sigma receptors, they have been proposed as a potential drug target in various neuropsychiatric illnesses. Sigma receptors are believed to be possible drug targets in schizophrenia, depression and anxiety disorders, amnesic and cognitive disorders, stroke and neurodegenerative disorders, substance abuse and in various pain disorders [14, 15]. These have been proposed based on the following actions of sigma receptors [14, 16]:

1. Modulation of a number of central neurotransmitter systems, including glutamate/NMDA, serotonin, dopamine, noradrenalin among others
2. Modulation of intracellular messenger systems
3. Promotion of neuronal differentiation and anti-apoptotic action
4. Antidepressant actions of sigma1 receptor agonists
5. Role in enhancing neuronal survival in brain ischemia
6. Neuroplasticity and gene regulation

2. **In schizophrenia:** It has been hypothesized that treatment in patients, with non-specific prodromal symptoms for several years preceding the onset of frank psychosis, with antidepressants like fluvoxamine could halt the transition into frank psychosis via the role of sigma receptor agonism in neuro-protection and neuronal plasticity [17]. However, sigma 1 receptor antagonism is beneficial in management of psychosis and drugs that block sigma receptors have been proposed as novel antipsychotic candidates with better side effect profiles than the available typical and atypical antipsychotics [18].

3. In cognition: Sigma receptor agonists have been proposed as possible treatment options in memory deficits and cognitive disorders based on the anti-amnesic and neuro-protective effects of sigma 1 agonists [19]. Sigma-1 receptor agonists have been found to better cognitive abilities and have a neuro-protective action on target neurons [20].

4. In substance abuse: Sigma-1 receptors have recently become targets for treating substance abuse and dependence. In vivo preclinical studies have revealed that sigma receptor ligands ameliorate select behavioral effects of many drugs of abuse including cocaine, methamphetamine, ethanol and nicotine [21]. Strategies to reduce the access of cocaine to sigma receptors have included antisense oligonucleotides to the sigma-1 receptor protein as well as small molecule ligands with affinity for sigma receptor sites [22]. Studies have suggested that sigma receptors are involved in mechanisms of methamphetamine induced psychiatric complications and neurotoxicity [23]. Antagonists at these sigma receptor sites therefore have potential in the management and treatment of methamphetamine addiction.

5. In neuropathic pain: Sigma receptor antagonists are emerging targets for the treatment of neuropathic pain. Selective sigma 1 receptor antagonists are proposed as an option in treating neuropathic pain based on functional data in pain models and findings based on the study of sigma 1 receptor knock-out mice [24].

Conclusion

Sigma receptors mediate their action through multiple neurotransmitter systems. The focus of recent bio – molecular research has been on sigma receptors. Research in this area is likely to discover new and noble pharmaco-therapeutic agents for various neuropsychiatric disorders.

REFERENCES

1. Hayashi T, Su T. The sigma receptor: evolution of the concept in neuropsychopharmacology. Curr Neuropharmacol. 2005 Oct; 3(4):267-80. | 2. Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE. The effects of morphine- and nalorphine- like drugs in the nondependent and morphine-dependent chronic spinal dog. J Pharmacol Exp Ther. 1976 Jun; 197(3):517-32. | 3. Su TP. Evidence for sigma opioid receptor: binding of [3H]SKF-10047 to etorphine-inaccessible sites in guinea-pig brain. J Pharmacol Exp Ther. 1982 Nov;223(2):284-90. | 4. Largent BL, Gundlach AL, Snyder SH. Pharmacological and autoradiographic discrimination of sigma and phencyclidine receptor binding sites in brain with (+)-[3H]SKF 10,047, (+)-[3H]-3-[3-hydroxyphenyl]-N-(1-propyl)piperidine and [3H]-1-[1-(2-thienyl)cyclohexyl]piperidine. J Pharmacol Exp Therap. 1986;238:739–748. | 5. Largent,B.L., Gundlach AL, Snyder SH. Sigma receptors on NCB-20 hybrid neurotumor cells labeled with (+)[3H]SKF 10,047 and (+)[3H]3-PPP. Eur J Pharmacol. 1986;124:183–187. | 6. Hellewell SB, Bowen WD. A sigma-like binding site in rat pheochromocytoma (PC12) cells: decreased affinity for (+)-benzomorphans and lower molecular weight suggest a different sigma receptor form from that of guinea pig brain. Brain Res. 1990;527:244–253. | 7. Seth P, Ganapathy ME, Conway SJ, Bridges CD, Smith SB, Casellas P, Ganapathy V. Expression pattern of the type 1 sigma receptor in the brain and identity of critical anionic amino acid residues in the ligand-binding domain of the receptor. Biochim Biophys Acta. 2001;1540:59–67. | 8. Kitaichi K, Chabot JG, Moebius FF, Flandorfer A, Glossmann H, Quirion R. Expression of the purported sigma(1) (sigma(1)) receptor in the mammalian brain and its possible relevance in deficits induced by antagonism of the NMDA receptor complex as revealed using an antisense strategy. J Chem Neuroanat. 2000 Dec;20(3-4):375-87. | 9. Palacios G, Muro A, Vela JM, Molina-Holgado E, Guitart X, Ovalle S, Zamanillo D. Immunohistochemical localization of the sigma1-receptor in oligodendrocytes in the rat central nervous system. Brain Res. 2003 Jan 24;961(1):92-9. | 10. Niitsu T, Iyo M, Hashimoto K. Sigma-1 receptor agonists as therapeutic drugs for cognitive impairment in neuropsychiatric diseases. Curr Pharm Des. 2012;18(7):875-83. | 11. Stahl SM. The Sigma Enigma: Can Sigma Receptors Provide a Novel Target for Disorders of Mood and Cognition? J Clin Psychiatry. 2008 Nov;69(11):1673-4. | 12. Nuwayhid SJ, Werling LL. Sigma1 receptor agonist-mediated regulation of N-methyl-D-aspartate-stimulated [3H]dopamine release is dependent upon protein kinase C. J Pharmacol Exp Ther. 2003 Jan;304(1):364-9. | 13. Bermack JE, Debonnel G. Modulation of serotonergic neurotransmission by short- and long-term treatments with sigma ligands. Br J Pharmacol. 2001;134:691–699. | 14. Skuza G. Pharmacology of sigma (σ) receptor ligands from a behavioural perspective. Curr Pharm Des. 2012;18(7):863-74. | 15. Hayashi T, Su TP. An update on the development of drugs for neuropsychiatric disorders: focusing on the sigma 1 receptor ligand. Expert Opin Ther Targets. 2008 ;12(1):45-58. | 16. Hayashi T, Su TP. Sigma-1 receptor ligands: potential in the treatment of neuropsychiatric disorders. CNS Drugs. 2004;18(5):269-84. | 17. Hashimoto K. Can the sigma-1 receptor agonist fluvoxamine prevent schizophrenia? CNS Neurol Disord Drug Targets. 2009;8(6):470-4. | 18. López-Muñoz F, Álamo C. Neurobiological background for the development of new drugs in schizophrenia. Clin Neuropharmacol. 2011;34(3):111-26. | 19. van Waarde A, Ramakrishnan NK, Rybczynska AA, Elsinga PH, Ishiwata K, Nijholt IM, Luiten PG, Dierckx RA. The cholinergic system, sigma-1 receptors and cognition. Behav Brain Res. 2011;221(2):543-54. | 20. Antonini V, Marrazzo A, Kleiner G, Coradazzi M, Ronsisvalle S, Prezzavento O, Ronsisvalle G, Leanza G. Anti-amnesic and neuroprotective actions of the sigma-1 receptor agonist (-)-MR22 in rats with selective cholinergic lesion and amyloid infusion. J Alzheimers Dis. 2011;24(3):569-86. | 21. Robson MJ, Noorbakhsh B, Seminerio MJ, Matsumoto RR. Sigma-1 receptors: potential targets for the treatment of substance abuse. Curr Pharm Des. 2012;18(7):902-19. | 22. Narayanan S, Mesangeau C, Poupaert JH, McCurdy CR. Sigma receptors and cocaine abuse. Curr Top Med Chem. 2011;11(9):1128-50. | 23. Kaushal N, Matsumoto RR. Role of sigma receptors in methamphetamine-induced neurotoxicity. Curr Neuropharmacol. 2011;9(1):54-7. | 24. Díaz JL, Zamanillo D, Corbera J, Baeyens JM, Maldonado R, Pericàs MA, Vela JM, Torrens A. Selective sigma-1 (sigma1) receptor antagonists: emerging target for the treatment of neuropathic pain. Cent Nerv Syst Agents Med Chem. 2009;9(3):172-83. |