Review Article

CELLULAR AND MOLECULAR PHARMACOLOGY OF SIGMA RECEPTORS

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ABSTRACT

Sigma (σ) receptors were originally discovered in central nervous system of mammals. Two subtypes of sigma receptors were identified, sigma-1(σ_1) and sigma-2(σ_2). Sigma receptors are non-opiate and non-dopaminergic G-protein coupled receptor (GPCR) which interacts with psychotomimetic drugs like benzomorphan, haloperidol, fluphenzine and many more. The sigma receptors are mainly expressed in brain, heart, liver, spleen, GI tract, blood cells and endocrine tissues. Tumor cells also contain high density of sigma receptors. Endogenous ligands for sigma receptors include divalent cations like magnesium, calcium, manganese, zinc, cadmium and copper. SKF-10,047 was first synthetic ligand for sigma receptor. σ_1 receptor expression was found to be predominate over σ_2 receptor subtype. σ receptors can control the modulation of voltage gated Ca^{++} channel in neuronal and non-neuronal cells. Sigma receptors were reported to increase the force of contraction of heart. It can control various neurotransmitter system including glutamatergic, cholinergic, opioidergic and catecholaminergic and important role in various disorders like schizophrenia, pain, cardiovascular diseases and cognitive disorder. The expression of sigma receptors on tumor cells indicates the role in pathogenesis of cancer. Several drugs of abuse have affinity for σ sigma receptors indicate the role in abuse. σ receptors also interact directly or indirectly with opiate receptors and modulate the analgesic effect of opioids. Sigma receptors are located in gastro-intestinal tract and have protective effect in duodenal ulcer.

Keywords: Sigma receptors, G-protein coupled receptor, Calcium signaling, Neurotoxicity, Cancer, Cognitive disorder, Drug abuse.

CELLULAR AND MOLECULAR PHARMACOLOGY OF SIGMA RECEPTORS

HISTORICAL PERSPECTIVE

σ Receptors were first proposed in 1976 by Martin and co-workers based on the actions of SKF-10,047 (N-allylnormetazocine) and related benzomorphans. The name σ was in fact derived from the first letter "S" from SKF-10,047 which was thought to be the prototypic ligand for these receptors. SKF-10,047 interacts with a number of distinct binding sites, leading to much confusion about the true identity and nature of σ receptors during its early history. σ Receptor were originally thought to be a type of opioid receptor. This belief stemmed from a historic study by Martin and colleagues who evaluated SKF-10,047 and other benzomorphans in morphine-dependent and non-dependent chronic spinal dogs. In this groundbreaking study, Martin and colleagues discovered that the physiological actions of the tested compounds fell into three distinct groups. They hypothesized that the differences between the groups stemmed from interactions with different subtypes of opioid receptors[1]. Martin's study employed the use of racemic benzomorphans, a mixture of the (+) and (-)-isomers of the compounds. Therefore, in later studies, when the isomers of benzomorphans were evaluated separately, it was determined that the (-)-isomers accounted for the vast majority of opioid-mediated effects. During the 1980s, renewed interest in the (+)-isomer of SKF-10,047 occurred when it was determined that it possessed phencyclidine (PCP)-like properties. During this period, the term σ /PCP made its appearance in the literature and many investigators believed that the σ and PCP sites were identical. There was conclusive evidence that (+)-SKF-10,047 interacted with the PCP binding site, which was ultimately determined to be within the ionophore of the N-methyl-D-aspartate (NMDA) receptor[2,3]. However, as selective ligands for the NMDA receptor were identified, it became apparent that [^{3}H](+)-SKF-10,047 binding could only be partially displaced using selective NMDA receptor ligands[4]. Therefore, it appeared that (+)-SKF-10,047 bound to another site in addition to the ionophore of the NMDA receptor. This other binding site was ultimately identified as the entity that today retains the designation of the σ receptor. Some selected compounds having affinity for σ receptor include, (+)-Pentazocine, Dextrallorphan, (+)-Cyclazocine, (+)-SKF-10,047, Haloperidol, Fluphenazine, Perphenazine, Pyrilamine, Chlorpheniramine and many more[5].

σ RECEPTOR SUBTYPES

There are two well established subtypes of σ receptors, which have been designated σ_1 and σ_2. These receptor subtypes can be distinguished from one another based on their molecular weights, tissue distribution, and drug selectivity patterns. Select features of these two subtypes and compounds that are commonly used as agonists and antagonists at σ receptors are summarized in Table 1.

σ Receptors are found in a variety of cell types that are not components of organs. Naturally occurring cells such as blood cells and tumor cells contain significant levels of σ receptors. Blood cells that express σ receptors include peripheral blood leukocytes, granulocytes, lymphocytes

and natural killer cells[12]. Tumor cells also contain high densities of σ receptors, and recent studies report that they are expressed in high densities on proliferating tumors[13,14]. The expression of the σ_1 subtype appears to predominate over the σ_2 subtype. σ_1 Receptors appear to translocate during signaling and are linked to the modulation or production of intracellular second messengers. In addition, σ_1 receptors can associate with other proteins, including ankyrin B, heat shock protein 70 (hsp70), heat shock conjugate protein (hsc 70), glucose-related protein (GRP78/BiP) and potassium channels[15,16]. The σ_2 subtype appears to be a distinct physical entity from the σ_1 receptor. Comparisons of their sizes based on affinity labeling studies indicated that the σ_2 subtype is slightly smaller than the σ_1 receptor[17]. The sequence of the σ_2 receptor has not yet been determined, although considerable progress has been made in this area in recent years. In contrast to σ_1 receptors that readily translocate, σ_2 receptors appear to be lipid raft proteins that affect calcium signaling via sphingolipid products[18]. In addition to σ_1 and σ_2 receptors, numerous papers have cited evidence in support of additional subtypes. However, these putative subtypes have not yet been well characterized and will therefore not be described here in detail.

Table 1: Distinguished features of σ receptor sub-types

FEATURES	σ_1 RECEPTOR	σ_2 RECEPTOR
Molecular weight[6]	25-29 kDa	18-22 kDa
Tissue distribution[7]**:**		
Brain	High	High
Heart	High	Low
Liver	High	High
Spleen	High	Low
GI tract	High	High
Agonist (IC_{50} in nM)[3,8,9]**:**		
DTG (di-o-tolylguanidine)	74 ± 15	61 ± 13
(+)-Pentazocine	7 ± 1	1361 ± 85
Igmesine	Not determined	Not determined
(+)-SKF-10,047	29 ± 3	33,654 ± 9409
Antagonist (IC_{50} in nM)[10,11]**:**		
BD1063	9 ± 1	449 ± 11
1-[2-(3,4-dichlorophenyl)ethyl]-4-methyl piperazine		
NE100	2 ± 0.3	85 ± 33
N,N-dipropyl-2-[4-methoxy-3-(2-phenylethoxy) phenyljethylamine		
Panamesine	Not determined	Not determined

ENDOGENOUS LIGAND(S)

The conclusive identification of an endogenous ligand for σ receptors has yet to be achieved. This section summarizes data supporting the existence of an endogenous ligand for these receptors, and raises the possibility of such compounds.

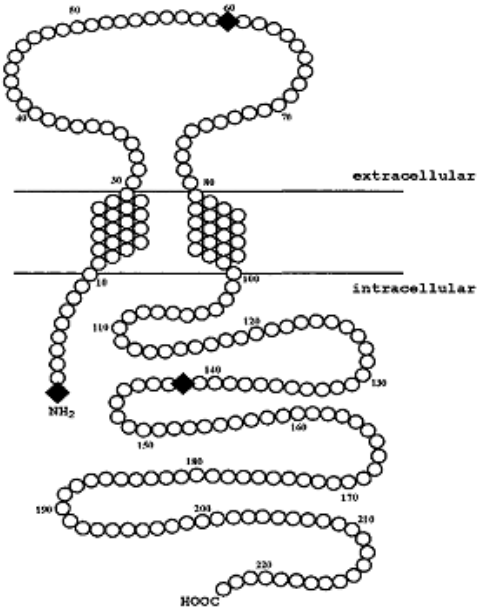
Receptor binding studies to identify known endogenous ligands with significant affinity for σ receptors have been employed by a number of investigators. Although the vast majority of known endogenous compounds exhibit low to negligible affinities for σ receptors, some activity has been described below in further detail. Su and coworkers were the first to suggest that some neurosteroids serve as endogenous ligands for σ receptors. In particular, progesterone was shown to exhibit nanomolar affinity for σ receptors in guinea pig brain and spleen. The interaction of progesterone with brain σ receptors was competitive in nature, suggesting that progesterone binds to the same portion of the receptor as classical σ ligands[19]. Neuropeptide Y has been reported to have significant affinity for σ receptors[20]. However, subsequent efforts to confirm this interaction have been unsuccessful. It therefore does not appear that neuropeptide Y is an endogenous ligand for σ receptors. A number of investigators have shown that divalent cations significantly inhibit radio-ligand binding to σ receptors. These divalent cations include magnesium, calcium, manganese, zinc, cadmium, copper[21,22].

STRUCTURE OF σ RECEPTOR

Sigma (σ) receptors are defined as non-opiate, non-dopaminergic and non-phencyclidine binding sites which interact with several psychoactive agents including benzomorphans, haloperidol and phencyclidine[23]. These receptors are expressed in various tissues associated with endocrine, immune and nervous systems. Multiple functions in multiple organs suggest that the σ receptors may play a fundamental role in modulating a wide variety of responses in different tissues[24]. The sequence of the σ_2 receptor has not yet been determined, although considerable progress has been made in this area in recent years and will not be described here in detail.

The four different mammalian σ_1 receptor proteins (guinea pig, human, mouse and rat) thus far cloned all consists of 223 amino acids (See figure 1). The amino acid sequence is highly similar across different species. There is no other mammalian protein thus far known that shows significant structural homology to the σ_1 receptor. Among non-mammalian proteins, the fungal ERG2 protein from different organisms (S. cerevisiae, N. crassa, M. grisea, S. pombe and U. maydis) exhibits significant structural homology with the mammalian σ1 receptor[25]. The mammalian σ_1 receptor is undoubtedly an integral membrane protein. The cloned human σ_1 receptor has been shown to localize to nuclear and endoplasmic reticulum membranes[26].

Figure 1: Topology of the σ receptor[25]



[The accessibility of various parts of the receptor indicate that the σ receptor forms two membrane spanning helices, with cytoplasmic N- and C-terminal and an extracellular loop.]

PHARMACOLOGICAL ROLE OF SIGMA RECEPTORS

Many of the proposed functions of σ receptors relate to electrical excitability. At the cellular level, σ receptors modulate action potential firing in neurons and contraction of various kinds of muscle fibers[27,28]. σ Receptors have been implicated in the modulation of the release of dopamine[29], acetylcholine[30] and glutamate[31]. σ Receptor ligands have neuroprotective and anti-amnesic activity[32]. A link between σ receptors and schizophrenia has been implied by some studies of σ receptors, and by the antipsychotic and psychotomimetic actions of σ receptor ligands[8]. Functions for σ receptors in endocrine and immune systems have also been suggested[33,34]. σ Receptors are present in excitable cells such as neurons, heart muscle cells and endocrine cells, as well as non-excitable tissues such as liver and kidney[35]. σ Receptors are also implicated in cancer cell biology[36], although the molecular mechanisms are unknown. Among the many functions attributed to σ receptors, some clearly have electrical manifestations. In others the electrical dimension is more remote, but ion channel involvement remains a possibility. Ion channels represent important functional targets of σ receptors.

Moleculare interactions between σ receptors and various ion channels

Many of the proposed functions of σ receptors relate to electrical excitability. At the cellular level, σ receptors modulate action potential firing in neurons and contraction of various kinds of muscle fibers[27,28]. Three distinct potassium channels, the channel underlying the M-current, the channel underlying a calcium-activated potassium current and the channel underlying the A-current were all inhibited by 3-PPP. These channels exhibited different sensitivities to 3-PPP in the order M-current > calcium-activated potassium current > A-current. The modulation of multiple channel types by σ receptors is a recurring theme in σ receptor physiology. The peptidergic nerve terminals of the rat neurohypophysis contain three distinct types of potassium channel with roles in the regulation of neuropeptide release[37]. Two of these, a large conductance calcium-activated potassium channel and a potassium channel underlying a transient A-current, were reversibly inhibited by the a receptor specific agonists SKF-10,047, pentazocine, and DTG (1,3-di-o-tolylguanidine) as well as the nonspecific a receptor ligands haloperidol and apomorphine[38].

A number of studies have implicated σ receptors in various forms of calcium signaling in both neuronal and non-neuronal cells[39-41]. A series of σ receptor ligands was tested for modulation of voltage-gated Ca^{+2} channels in cultured hippocampal pyramidal neurons. Although many ligands strongly inhibited multiple subtypes of Ca^{+2} channels, the rank order of potency showed a marked departure from the rank order of σ receptor binding, indicating that a receptors could not account for all of these actions. A recent study in intra-cardiac and superior cervical ganglia indicated that σ receptors modulate multiple types of voltage-gated Ca^{+2} channels in both sympathetic and parasympathetic neurons[42]. The high potency of ibogaine suggested that these responses were mediated by σ_2 receptors.

Ion channels can be modulated by a vast number of receptor types, and the transduction mechanisms are the subject of an enormous body of research. The overwhelming majority of these cases follow a few basic mechanistic patterns involving activation of G proteins or protein kinases or both in combination. More recently, signal transduction mechanisms have been identified in which ion channels can be modulated by phospholipids such as phosphatidyl inositides and reactive gases such as nitric oxide. The unique molecular structure of the σ receptor defies classification along the lines of established transduction mechanisms, and raises the question of whether σ receptors employ novel

mechanisms to modulate ion channels. Although some evidence suggests that σ receptors can modulate responses mediated by second messenger systems, the direct transduction pathway employed by σ receptors remains unclear[43,44]. Some authors hypothesized that the σ_1 receptor functionally interacts with G proteins through a mechanism that differs from that of classical G protein coupled receptors[45].

σ receptors and modulation of classical neurotransmitter system

Several neurotransmitter systems have been found to be modified by σ ligands, including catecholaminergic, glutamatergic and opioidergic systems. Cell firing, neurotransmitter uptake, release and signaling including intracellular calcium homeostasis have been studied.

On glutamatergic neurotransmission

Debonnel and deMontigny have described in detail the modulation of N-methyl-D-aspartate (NMDA)-induced electrophysiological responses by σ receptors[46]. They have shown that application of σ receptors ligands enhances the responsiveness of pyramidal neurons in hippocampal regions to applications of NMDA[47]. Several σ receptor ligands have also been found to protect against NMDA-induced neurotoxicity in several models, including primary cultures of rat cortical neurons[48] and organotypic dopaminergic midbrain slice cultures[49]. Exactly how modification of the NMDA receptor-mediated response is achieved by σ ligands is not known.

On cholinergic neurotransmission

Evidence links σ receptor activity to regulation of cholinergic processes, including cognition and memory. Subcutaneous application of the σ receptor agonists (+)-SKF-10,047 as well as DTG has been shown to enhance the release of acetylcholine from prefrontal cortex measured by microdialysis[50]. Data suggest that the behavioral effects of σ ligands in cognition are likely to be grounded to a large extent in their ability to regulate cholinergic systems. This indicates enormous therapeutic potential in the areas of Alzheimer's, possibly other forms of dementia, and cognitive enhancement in general[51].

On opioidergic neurotransmission

Although σ receptors were initially thought to be members of the opioid receptor family, they were later recognized as naltrexone-insensitive. Despite some lingering confusion, σ receptors are now not generally considered opioid. The exception to this rule is exemplified by recent studies from Tsao and Su[52], who purified a naloxone- and haloperidol-sensitive binding site from rat liver and brain. Couture and Debonnel[53] found some evidence for potential involvement of this unique site in some electrophysiological responses to (+)-pentazocine, but not to other prototypical σ_1 receptor ligands. However, for the most part, the majority of σ receptors appear not to share opioid receptor properties. While there are apparently very few, if any, studies on direct interactions between σ receptors and opioid pathways that explore the relationship at a neurochemical level, σ receptors have been shown to have an anti-opioidergic action[54]. While there is relatively little biochemical data on opioid/σ interactions, the behavioral data from analgesia studies are provocative and could provide important new approaches to pain management.

On catecholaminergic neurotransmission

Dopamine is a major transmitter in motor and limbic pathways. The substantia nigra and the nucleus accumbens have significant numbers of σ receptors. Many antipsychotics and experimental antipsychotics have σ receptor antagonist properties. Regulation of dopaminergic activity has obvious clinical potential in the treatment of schizophrenia and motor function. σ Receptor ligands have been tested for their effects on dopaminergic neuronal activity as well as dopamine release. Many of these studies have employed peripheral administration of σ ligands coupled with measurement of central activity, which is critical for therapeutic development, but does not address mechanism of action. Intra-peritoneal injection of the σ receptor agonists (+)-pentazocine and (+)-SKF-10,047 were shown to increase dopamine release in the striatum and prefrontal cortex[55].

Noradrenergic pathways arise from locus coeruleus and terminate in hippocampus, cortex, and cerebellum. The effects of σ receptor agonists on NMDA-stimulated release of [^{3}H]norepinephrine from terminal fields of locus coeruleus neurons was similar to that of σ agonists on dopamine release, i.e. σ agonists inhibited stimulated [^{3}H]norepinephrine release. (+)-pentazocine inhibited release from rat hippocampus in a concentration-dependent manner with IC50 values consistent with actions via σ_1 and σ_2 receptors[56]. Inhibition was reversed by σ receptor antagonists, supporting a role for both σ_1 and σ_2 receptors in regulation of release.

In conclusion, the relationship of σ receptors to the dopaminergic and noradrenergic systems indicates that σ receptors could have key roles in depression and schizophrenia.

σ receptors and regulation of cell growth and implication in cancer

Several lines of evidence suggest that σ receptors, particularly σ_2 receptors, may be involved in regulation of cell proliferation and cell survival. σ Receptors are highly expressed in tumors and tumor cell lines of various tissue origins. σ Receptors were first reported in solid neural and non-neural tumors and were found to be more highly expressed than in surrounding normal tissue[57]. A preliminary report indicated that σ receptors were expressed in very high levels in breast tumor biopsy samples, while surrounding normal tissue taken at the same time showed no detectable σa receptor binding activity[58]. Many evidence suggested that σ receptor subtypes are present in neuroblastomas, gliomas,

melanomas and in breast, prostate, lung and leukemia cell lines[59].

Calcium is known to play an important role in regulation of cell proliferation. This calcium can cause induction of genes important for proliferation. High calcium levels can also cause mitochondrial dysfunction which leads to cell death. Direct effects on cell calcium occur when σ_2 receptors are activated by agonists. σ Ligand-induced increases in cytosolic free calcium in a breast adenocarcinoma and colon carcinoma cell line have also been reported. These effects were also likely mediated by σ_2 receptors, although the subtype involvement was not determined. Thus σ_2 receptors may utilize calcium signals in wide variety of cell types[60].

Ceramide is a sphingolipid second messenger that has been directly linked to regulation of cell growth. Depending on cell type, ceramide can either stimulate cell proliferation or cause inhibition of cell proliferation and induction of apoptosis. Ceramide can stimulate cell proliferation by downstream activation of the mitogen-activated protein (MAP) kinase pathway via ceramide-activated protein kinase (or kinase suppressor of ras). However, ceramide is most often associated with the induction of apoptosis. It has been reported that σ_2 receptor agonists increase the level of ceramide in breast tumor cell lines[61]. More work will be required to identify the targets of ceramide in cells treated with σ_2 agonists, but ceramide formation is likely to play a key role in σ_2 receptor-mediated apoptosis.

The development of drug resistance presents an enormous problem in cancer chemotherapy. Tumor cells develop resistance to anti-neoplastic agents via several mechanisms. These include mutations in p53, aberrations in caspase function and over-expression of drug efflux pumps[62]. It has been reported that agonist activation of σ_2 receptors results in induction of apoptosis in several breast tumor cell lines which are highly resistant to the apoptotic effects of other anti-neoplastic agents[63]. The mechanism is both caspase and p53-independent, thus resistant cells remain susceptible. It therefore may be possible to target σ_2 receptors for the development of novel anti-tumor agents effective against a variety of drug-resistant cells.

σ receptors and cognitive functions

Monnet et al[64] observed that selective σ receptor agonists potentiated the N-methyl-D-aspartate (NMDA)-induced neuronal activation and the importance of NMDA receptor activation in acquisition and learning processes, they tested the effects of systemic administration of a series of reference or selective σ ligands in a passive avoidance task in rats. The authors suggested from these initial observations the potential interest of selective σ compounds like igmesine for the treatment of cognitive dysfunctions, notably associated with aging or dementia. Even if, very few compounds are presently in clinical trials for cognitive indications, numerous studies have confirmed and analyzed the behavioral efficacy of σ_1 receptor ligands as anti-amnesic agents in pharmacological and pathological models.

Neuroactive steroids, i.e. both neuroactive circulating steroids and neurosteroids, modulate neuronal activity rapidly through nongenomic actions and affect learning and memory processes, mood or depression. Pregnenolone, dehydroepiandrosterone (DHEA) and their sulfate esters are considered as excitatory steroids since they act as negative modulators of γ-aminobutyric type A ($GABA_A$) receptors[65] and positive modulators of NMDA receptors[66]. Pregnenolone, dehydroepiandrosterone (DHEA) and their sulfate esters are also interact with σ_1 receptors.

Acetylcholine and its nicotinic or muscarinic receptors play an important role in memory processes. Groups of cholinergic basal forebrain neurons, originating from the nucleus basalis magnocellularis (NBM) and innervating the cerebral cortex, amygdaloid complex, or hippocampal formation, are involved in learning and memory formation. Patients suffering from Alzheimer's disease, or related dementia, elicit profound degeneration and dysfunction in cortical cholinergic activity, assumed to be partly responsible for the course of memory deficits observed in Alzheimer's disease[67,68]. Acetylcholinesterase inhibitors, such as tacrine or physostigmine, exert some beneficial effects in several animal amnesia models[69] and in some Alzheimer's disease patients[70]. The NMDA receptors mediate the induction of different forms of synaptic plasticity, such as long-term potentiation (LTP) or long-term depression (LTD). These forms of cerebral plasticity are considered to play a critical role in the stabilization/consolidation of synapses in particular brain structures, sustaining learning and memory processes. The modulation exerted by σ_1 agonists on several responses induced by NMDA receptor activation, particularly in the hippocampus, is now well documented, although the exact mechanism remains to be characterized[71].

σ receptors and schizophrenia

Certain symptoms of schizophrenia, primarily the called negative symptoms and the cognitive deficits are less responsive to treatment with dopamine antagonists than positive symptoms of the illness. This suggests that some of the central symptoms of schizophrenia may be less related or unrelated to an increase in dopaminergic function. Moreover, σ receptors have generated a great deal of interest because of their possible roles in various behaviors, including depression, anxiety, learning processes and psychosis. The potential involvement of σ receptors in the pathophysiology of schizophrenia was originally proposed when it was discovered that synthetic σ ligands exhibited psychotomimetic properties and because several neuroleptic drugs have high affinity for σ receptors. It is important to note that there is an intricate relationship between σ receptors and dopamine and glutamate neurotransmitter systems[72]. However, no correlation between the affinity of neuroleptics for σ

receptors and their therapeutic efficacy has been found. Thus, it has been suggested that σ receptors may instead mediate the motor side effects of antipsychotic drugs. Recently, the relationship between the ability of neuroleptics to interact with σ_1 and σ_2 receptors and their tendency to induce dystonic reactions in humans was evaluated. The findings suggested that the motor side effects induced by neuroleptics could be mediated through both σ_1 and σ_2 receptors[73]. However, certain pharmacological studies have reported a lack of correlation between behavioral effects of antipsychotic drugs in animal models of schizophrenia and affinity for σ receptor[74].

σ receptors and drug abuse

Many drugs of abuse interact with σ receptors, providing a logical target for medication development. Drugs of abuse with significant affinities for σ receptors include some opiates, cocaine, amphetamines and phencyclidine (PCP). In addition, the actions of other abused substances such as alcohol and nicotine can be modulated by σ receptor ligands, even if the abused substances themselves do not bind to these receptors[75]. The mechanisms through which σ receptors influence the actions of drugs of abuse are diverse. These mechanisms can be divided into three categories. First, drugs of abuse can directly bind to σ receptors: cocaine, methamphetamine, methylene-dioxy-methamphetamine (MDMA) and phencyclidine. Many of these abused substances have preferential affinity for σ_1 receptors, which is the subtype that has been primary focus of many recent studies[75]. Secondly, σ receptor mediated modulation of other neurotransmitter system. Most drugs of abuse also interact with various neurotransmitter systems such as dopamine[76], serotonin[77] and glutamate[78] to influence brain physiology and behaviors. In addition to modulating the activity of dopaminergic, serotonergic and/or glutamatergic neurotransmission through post-synaptic mechanisms, the interaction of drugs of abuse with σ receptors may also alter pre-synaptic mechanisms that are involved in the synthesis and release of classical neurotransmitters[79]. Third, σ receptor-induced changes in gene expression have focused on immediate early genes, particularly those of the fos family of transcription factors[80]. These changes are significant because increases in immediate early gene expression by drugs of abuse may be the initial step by which these drugs alter the expression of late genes to produce enduring effects on nervous system function.

σ_1 receptor and modulation of opiate analgesics

Pentazocine is widely used clinically as an opiate analgesic and is provided as a racemate of both (+) and (-) isomers. Like many other opiates, the (-) isomer has high affinity for opioid receptors, particularly μ and K binding sites hence it is effective analgesic. In contrast, (+)-pentazocine do not have high affinity to opioid receptors hence alone had no analgesic action but it does display high affinity for σ_1 receptors. However, when co-administered with an active opiate analgesic (morphine), (+)-pentazocine effectively lowered the analgesic responses[81]. Here, both supraspinal and spinal morphine analgesia is effectively reduced by (+)-pentazocine. The ability of (+)-pentazocine to modulate morphine actions was limited to analgesia. Haloperidol, a known antagonist of σ_1 and D_2 receptor, alone potentiated the actions of morphine. More important, haloperidol also enhanced the response to morphine administered with (+)-pentazocine. Thus, haloperidol completely reversed the actions of (+)-pentazocine. Indeed, it is not even known whether or not σ receptors interact directly with opioid receptors or modulate pathways downstream from the opioids[82].

σ receptors and modulation of immune system

σ receptor expression in the immune system has not yet been exhaustively characterized at the mRNA or protein level. Nevertheless, a few studies have unequivocally demonstrated the presence of σ receptors in different immune tissues. Their presence was first reported by De Souza et al. in rat spleen[83], by Su et al. in guinea pig spleen[19] and by Wolfe et al. in human peripheral blood leukocytes[12]. Phencyclidine (PCP) binds with high affinity to both PCP and σ receptors and mediate immunosuppressive activities. These activities include mitogen-driven antibody production and lipopolysaccharide-driven interleukin-1 production[84]. The mechanism by which σ ligands produce their immunosuppressant effects is unknown.

σ receptors and gastrointestinal functions

σ receptors are located in the gastrointestinal tract of the guinea pig particularly dense distribution in the mucosa and in the sub-mucosal layer of esophagus, fundus, pylorus, duodenum, ileum and colon[85] σ ligands have been found able to stimulate mucosal alkaline secretion and this effect has been demonstrated to correlate with their protective effects on experimental duodenal ulcers[86]. (+)-SKF-10,047, DTG and igmesine stimulated colonic postprandial motility and increased proximal colonic motility indexes in dose-related manner[87]. This result suggests that σ ligands may be useful drugs specifically for enhancing postprandial colonic motility in patients with the irritable bowel syndrome with abnormally low postcibal motility.

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