Sigma Receptors and Cancer: Possible Involvement of Ion Channels

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Abstract

The sigma (σ) receptor and its agonists have been implicated in a myriad of cellular functions, biological processes and diseases. Whereas the precise molecular mechanism(s) of σ receptors and their involvement in cancer cell biology have not been elucidated, recent work has started to shed some light on these issues. A molecular model has been proposed for the cloned σ1 receptor; the precise molecular nature of the σ2 receptor remains unknown. σ receptors have been found to be frequently upregulated in human cancer cells and tissues. σ2 receptors drugs particularly have been shown to have antiproliferative effects. An interesting possibility is that σ and/or σ1 drugs could produce anticancerous effects by modulating ion channels. As well as proliferation, a variety of other metastatic cellular behaviors such as adhesion, motility, and secretion may also be affected. Other mechanisms of σ receptor action may involve interaction with ankyrin and modulation of intracellular Ca2+ and sphingolipid levels. Although more research is needed to further define the molecular physiology of σ receptors, their involvement in the cellular pathophysiology of cancer raises the possibility that σ drugs could be useful as novel therapeutic agents.

Introduction

The σ receptor was first described as a novel opioid receptor but was later found to be a distinct pharmacological entity distinguished by its unusually promiscuous ability to bind a wide variety of drugs (1). Although the molecular function of the σ receptors are not yet fully defined, and the natural ligand(s) is still not known, there is increasing evidence that σ receptors could play a significant role in cancer biology (2). Binding of antipsychotic drugs such as haloperidol, along with a genetic linkage to schizophrenia, implicate σ receptors also in psychosis (3). In the central nervous system, σ receptors have been shown to be involved in regulation of neurotransmitter release, modulation of neurotransmitter receptor function, learning and memory processes, and regulation of movement and posture (4, 5). Additional functions of σ receptors in motor, endocrine, and immune systems have also been suggested (6). Whereas lack of information about the precise molecular mechanism(s) of σ receptors has hindered elucidation of its potential functional role, recent research has begun to shed some light on this area of investigation. This review attempts to draw together our knowledge of the molecular biology and cellular physiology of σ receptors and their involvement in cancer. Thus, we hope to demonstrate how further investigation into σ receptor biology may provide insight into the potential use of the σ receptors and their associated drugs in diagnosis and therapy of cancer. In particular, we highlight a possible association of σ receptors with ion channels.

Pharmacology of σ Receptors

Endogenous ligands for σ receptors are not known, and it has been proposed that steroid hormones such as progesterone or testosterone may interact with them (7–9). Wilke et al. (10) used σ receptor modulation of ion channels in rodent neurohypophysial nerve terminals to investigate this question. Fifteen candidate endogenous σ receptor ligands, including biogenic amines (e.g., dopamine and serotonin), steroids (e.g., progesterone), and peptides (e.g., neuropeptide Y), were screened for electrophysiological activity at the σ receptor, but all gave negative results. The present classification of σ receptor ligands is based on their differential ability to bind a range of drugs (Table 1). σ receptor ligands appear to have heterogeneous chemical structures, and some are analogous to well-known psychotropic drugs. Pharmacological studies have identified two subtypes of σ receptor, termed σ1 and σ2 (Table 1). A third subtype of σ receptor has also been proposed (11). However, the σ1 receptor is the most documented of these subtypes to date.

Molecular Characterization of σ Receptors

σ1 Receptor. The gene encoding the σ1 receptor has been cloned and shown to be distinct from any known receptor class (12, 13). The 25,300 kDa protein product of this gene was reported to lack significant homology with known mammalian proteins, but to possess some homology with fungal sterol isomerases. The σ1 gene has been isolated from guinea pig, human, mouse, and rat (12–14). The gene is approximately 7 kbp long and contains four exons, interrupted by three introns. Exon 3 is the shortest (93 bp), and exon 4 is the longest (1132 bp). Among the introns, intron 3 is the longest (~1250 bp). Exon 2 codes for the single transmembrane domain present in the receptor (15). In humans, the gene for the σ1 receptor is located on chromosome 9p13, a region associated with psychiatric disorders (15). A splice variant of the σ1 receptor has been found in Jurkat cells (16) and in mice (17). Interestingly, σ1 receptor splicing variants have been reported to display σ2 characteristics (18).

σ1 Receptor Mouse Knockout. Recently, a σ1 receptor mouse knockout has been generated to investigate its in vivo relevance (19). Homologous mutant mice were found to be viable and fertile, and did not display any overt phenotype (19). A significant decrease in the hypermotility response was measured on treatment with (+) SKF-10047, thereby strengthening claims for a role of the σ1 receptor in psychostimulant action (19).

Molecular Structure of the σ1 Receptor Protein. Initial hydrophy analysis of the deduced amino acid sequence of the σ1 receptor suggested a single transmembrane segment (12–14). Subsequently, Aydar et al. (20) have presented evidence that the σ1 receptor has two transmembrane segments that are localized to the plasma membrane (when expressed in Xenopus laevis oocytes) with the NH2 and COOH termini on the cytoplasmic side of the membrane (20). This approach led to the proposal of a model for the molecular structure of the σ1 receptor, as shown in Fig. 1 (20).

Mutational Studies of the σ1 Receptor. Because a splice variant of the σ1 receptor that lacks exon 3 does not have the ability to bind σ ligands, the ligand-binding domain with its critical anionic amino...
acid residues is likely to be in or around the region coded by exon 3 (16). The human σ1 receptor was individually mutated for each of the anionic amino acids in this region, heterologously expressed in MCF-7 cells, and the influence of each mutation on ligand binding was assessed (21). These studies identified two anionic amino acids, D126 and E172, that were obligatory for ligand binding. Although the ligand-binding function was abolished by either of these two mutations, expression of the mutants was normal at protein level. However, it is still possible that these mutations caused the σ1 receptor to be mislocalized or misfolded; therefore, this finding should be treated with some care. The model of the σ1 receptor (Fig. 1) would place the proposed ligand binding domain in the COOH-terminus intracellular portion, beyond the proposed second transmembrane domain (20). Accordingly, Wang et al. (18) have reported that splice variants that have lost one or more of these amino acids, not only lose σ1 binding but acquire σ2 binding characteristics. More in-depth molecular investigation of the σ1 receptor is necessary, however, to understand how its molecular structure relates to its diverse functional roles.

**The σ2 Receptor.** The molecular nature of the σ2 receptor is still unknown, despite apparent high densities of σ1 and σ2 receptor drug binding found in some tissues e.g., liver (22). A photoaffinity labeling study using DTG (a σ1 and σ2 receptor drug) revealed the existence of two protein bands of Mr 25,000 and 21,500 (22). Because the σ1 receptor was subsequently cloned (13) and shown to be a protein of Mr 25,300, it has been presumed that the σ2 receptor gene encodes a protein of Mr 21,500. Despite repeated efforts, however, the gene for the σ2 receptor remains unidentified. It has been suggested that the σ2 characteristics are, in fact, a consequence of σ1 gene alternative splicing (18). However, in the σ1 receptor knockout mouse, although σ1 receptor-specific drug binding was significantly reduced, binding of nonspecific σ drugs (DTG) was unaffected, suggesting that the σ2 receptor was unaffected (19). Additional studies are required to clarify this issue, e.g., by using photoaffinity studies with σ2 receptor-specific drugs to determine whether the second band observed in photoaffinity studies of liver with DTG are, in fact, the product of a specific σ2 receptor gene.

**Normal Tissue Distribution and Cellular Localization of σ Receptors**

σ1 receptors have been detected in different areas of the central nervous system, and in noneuronal cells, including at high levels in heart, ovary, kidney, testes, liver, and placenta (13, 19, 23, 24). High levels of σ1 receptors have also been found in embryonic stem cells and during all stages of embryogenesis (19). In developing embryos, σ1 receptors were detected within the central nervous system, along the developing spinal cord, in developing limbs at the branchial arches and inside the thoracic and abdominal cavities (19). On the other hand, little is, however, known about the tissue distribution of σ2 receptors. A variety of subcellular localization experiments have suggested the presence of σ1 receptors in the plasma membrane, mitochondria, and endoplasmic reticulum (20, 25–29). Interestingly, Hayashi and Su (25) recently found that σ1 receptors specifically

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### Table 1: Classification of commonly used σ receptor drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Alternative name</th>
<th>σ1 receptor affinity (nM)</th>
<th>σ2 receptor affinity (nM)</th>
<th>Authors classification of subtype selectivity</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)-pentazetine</td>
<td></td>
<td>17 (Ki)</td>
<td>6,611 (Ki)</td>
<td>Nonselective</td>
<td>87</td>
</tr>
<tr>
<td>N-allylnormetazetine</td>
<td>SKF-10047</td>
<td>597 (Ki)</td>
<td>39,740 (Ki)</td>
<td>σ1 receptor</td>
<td>87</td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
<td>6.44 (Ki)</td>
<td>221 (Ki)</td>
<td>Nonselective</td>
<td>87</td>
</tr>
<tr>
<td>1,3-di-(2-tolyl) guanidine</td>
<td>DTG</td>
<td>203 (Ki)</td>
<td>58.4 (Ki); 19 (Ki)</td>
<td>Nonselective</td>
<td>87, 89</td>
</tr>
<tr>
<td>Rimcazole</td>
<td>BW234U</td>
<td>1,460 (IC50)</td>
<td>1,460 (IC50)</td>
<td>Nonselective</td>
<td>90</td>
</tr>
<tr>
<td>R(+-)-3-hydroxyphenylpropylpiperidine</td>
<td>(+)-3-PPP</td>
<td>47 (Ki)</td>
<td></td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>Ifenprodil</td>
<td></td>
<td>2 (Ki)</td>
<td>5 (Ki)</td>
<td>Nonselective</td>
<td>92, 93</td>
</tr>
<tr>
<td>Iboagaine</td>
<td></td>
<td>31,696 (Ki)</td>
<td>963 (Ki)</td>
<td>σ2 receptor</td>
<td>95</td>
</tr>
<tr>
<td>5-(3-hydroxyphenyl)-2-methylmorphan-7-one</td>
<td>cB-184</td>
<td>7,436 (Ki)</td>
<td>13.4 (Ki)</td>
<td>Highly σ2 receptor specific</td>
<td>95</td>
</tr>
<tr>
<td>(+)-IR5R-E8-benzylidene-5-(3-hydroxyphenyl)-2-methylmorphan-7-one</td>
<td>cB-64D</td>
<td>3,063 (Ki)</td>
<td>16.5 (Ki)</td>
<td>Highly σ2 receptor specific</td>
<td>96</td>
</tr>
</tbody>
</table>

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**Fig. 1.** A structural model for the σ1 receptor. This model contains two transmembrane (TM) segments as determined by TM homology plots. The NH2 and COOH termini are shown on the intracellular side of the membrane, as deduced by the accessibility of green fluorescent protein tags to labeling when expressed in Xenopus oocytes. •, the two lysines in the guinea pig sigma receptor. In the rat sigma receptor, residue 60 is arginine; therefore, the only primary amino groups are lysine 142 and the terminal NH2 group. Their intracellular location in this model is consistent with poor biotin labeling in surface exposure studies before permeabilization of the Xenopus oocytes and efficient labeling thereafter. Figure has been used with permission of the authors Aydar et al. (20) and has been modified.
target neutral lipid-enriched subdomains on the endoplasmic reticulum membrane. The subcellular localization of α2 receptors is not known.

Expression of α Receptors in Tumor Cell Lines and Tissues. Both α receptor subtypes are highly expressed in tumor cell lines from various human cancer tissues, including small- and non-small-cell lung carcinoma (30–32), large-cell carcinoma (30), renal carcinoma (33), colon carcinoma (33), sarcoma (33), brain tumors (34), breast cancer (2, 32), melanoma (32), glioblastoma (32), and prostate cancer (32). Comparable findings available from rat cancer cell lines, such as C6 glioma (32), N1E-115 neuroblastoma (32), and NG108–15 neuroblastoma × glioma hybrid (32), generally agree with the human data (Table 2). Many of these observations are based on the binding of labeled α receptor drugs that are α1- or α2-receptor unspecific. In some cases, α1 sites were masked with dextrallorphan so as to determine the relative amounts of α1 and α2 sites in the cell preparations. However, these results await confirmation by Western blotting and reverse transcription PCR (RT-PCR) studies. A comparative study by Wheeler et al. (35) on mouse mammary adenocarcinoma revealed that proliferative cells possessed 10 times more α2 receptors than did quiescent cells. Zamora et al. (36) evaluated the density of α sites after the stimulation of mitosis and progression through the cell cycle in the human mammary tumor cell lines T47D and MCF-7 as well as in the prostate tumor cell line DU-145. The results suggested that both (a) there was a direct correlation between the binding of the α drug [N-[1’-2-piperidinyl(ethyl)]-4-[125]iodobenzamide (α2-selective) and, moderately selective for α1 receptors, and proliferative status; and (b) an up-regulation of α binding sites occurred before mitosis. Using N-[1’-2-piperidinyl(ethyl)]-3,12-diiodo-4 methoxybenzamide, also moderately selective for α1 receptors, another study also found that α and α1 receptors were present at high density on human breast tumor biopsies but virtually absent in normal tissues (37). Expression of α1 receptor, monitored immunocytochemically, has been suggested as a possible marker for predicting the aggressiveness of breast tumors, in particular, where there was a significant correlation between α1 receptor expression and progesterone receptor status (38).

α Receptor Drugs as Tumor Imaging Agents. The high densities of α1 and α2 binding sites in tumor cell lines and tissues are indicative of their involvement in the cellular pathophysiology of cancer and could have diagnostic potential in tumor imaging. Numerous preclinical studies have evaluated the usefulness of radiolabelled α drugs, as tumor imaging agents in melanoma (39–43), breast cancer (37, 44–49), prostate cancer (50, 51), and non-small-cell lung cancer in mouse tumor models (42). Generally, these observations suggested that α drugs could be effective ligands for tumor imaging, coupled with techniques such as positron emission tomography or single-photon emission computerized tomography (35, 36, 50, 52). Most of these α drugs are nonselective for the α1 and α2 receptors, but, more recently, α2-selective agents have shown the most promise in this regard (Refs. 44 and 45; Table 3).

Physiology and Pathophysiology of α Receptors

Effects of α Receptor Drugs on Cancer Cell Proliferation and Cell Death. Several studies have tested the potential effectiveness of α drugs on proliferation of tumor cells in vitro. Brent and Pang (33) studied the effects of various α drugs (e.g., haloperidol, DTG, SKF10047, pentazocine, and rimcazole) on the in vitro growth of human mammary adenocarcinoma, colon carcinomas, and melanomas in detail. Cellular proliferation was inhibited, and cell detachment and rounding subsequent to cell death were observed by light microscopy. Of the drugs tested, the α1- and α2-nonselective rimcazole and reduced haloperidol, which is the main metabolite of haloperidol in humans (54), were the most potent inhibitors of cell proliferation (53). Similar inhibitory effects of α drugs [e.g., N-[2-(piperidino) ethyl]-2-iodobenzamide (2-IBP), haloperidol, and 2-piperidinyl-(aminomethyl)-4-iodobenzamide (IPAB)] were observed on small-cell lung cancer (NCI-H209 and NCI-N417) cells (31). Importantly, IPAB or 2-IBP also inhibited the in vivo xenograft proliferation of NCI-N417 cells (31).

The question of the mechanism(s) underlying the inhibitory effect of α drugs on tumor cell proliferation is an important one. The morphological effect of treating C6 glioma cells with various α drugs (generally α1- and α2-nonselective) was examined (55). These drugs caused loss of cellular processes, assumption of spherical shape, and cessation of cell division; time course and magnitude of these effects were dependent on the concentration of the various α drugs used. Continued exposure to α drugs for 3–24 h resulted in cell death, although the morphological effects were reversible if the drug was removed shortly after rounding (55). Reduced haloperidol also potently inhibited proliferation of WI38 clone and MCF-7 breast adenocarcinoma cell lines; in these cells, the intracellular Ca2+ levels were raised, and apoptosis was observed (56), although a direct link between them was not shown. Crawford and Bowen (2) also demonstrated the ability of α2 drugs to induce cell death in the human breast tumor cell lines MCF-7, MCF-7/AdR−, T47D, and SKBr3. Both α2 subtype-specific and α2 nonselective drugs resulted in cell death by a mechanism that involved apoptosis. This was suggested to be a novel p53- and caspase-independent apoptotic pathway (57). The effects of α drugs on cell growth and apoptosis have been suggested to be through the sphingolipid pathway (57). Accordingly, α2 drugs applied to MCF-7/AdR− and T47D breast tumor cells induced dose-dependent

Table 2. Sigma receptor drug binding in tumor tissues and cell lines (from human, unless indicated otherwise)

<table>
<thead>
<tr>
<th>Cell line or tumor tissue</th>
<th>α receptor drugs tested</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-small-cell lung carcinoma</td>
<td>IPAB, haloperidol, DTG</td>
<td>30</td>
</tr>
<tr>
<td>Large-cell carcinoma (NCI-H1299 and NCI-H838)</td>
<td>IPAB, haloperidol, DTG</td>
<td>30</td>
</tr>
<tr>
<td>Lung cancer cell line (NCI-H4727)</td>
<td>IPAB, haloperidol, pentazocine, DTG (+/- dextrallorphan)</td>
<td>30, 32</td>
</tr>
<tr>
<td>Breast ductal carcinoma (T47D)</td>
<td>Pentazocine, DTG (+/- dextrallorphan)</td>
<td>32</td>
</tr>
<tr>
<td>Renal carcinoma</td>
<td>DTG</td>
<td>33</td>
</tr>
<tr>
<td>Colon carcinoma</td>
<td>DTG</td>
<td>33</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>DTG</td>
<td>33</td>
</tr>
<tr>
<td>Brain tumor tissue</td>
<td>DTG</td>
<td>34</td>
</tr>
<tr>
<td>(Nude mouse-bred) neuroblastoma and glioma</td>
<td>DTG</td>
<td>34</td>
</tr>
<tr>
<td>Rat neuroblastoma (NIE-115), rat glioma (cb)</td>
<td>Pentazocine, DTG (+/- dextrallorphan)</td>
<td>32</td>
</tr>
<tr>
<td>U-138MG glioblastoma</td>
<td>Pentazocine, DTG (+/- dextrallorphan)</td>
<td>32</td>
</tr>
<tr>
<td>Breast cancer cell line (MCF-7, T47D, and SKBr3)</td>
<td>Haloperidol, CB-64D, CB-184, IPAB</td>
<td>2, 36</td>
</tr>
<tr>
<td>Small-cell lung cancer (NCI-H209/N417)</td>
<td>IPB, haloperidol</td>
<td>31</td>
</tr>
<tr>
<td>Neuroblastoma [BE(2)] (SK-N-SH)</td>
<td>Pentazocine, DTG (+/- dextrallorphan)</td>
<td>32, 96</td>
</tr>
<tr>
<td>Prostate tumor cell line (DU-145) (LoCap)</td>
<td>IPAB, pentazocine, DTG (+/- dextrallorphan)</td>
<td>32, 36</td>
</tr>
<tr>
<td>Mammary adenocarcinoma (line 66)</td>
<td>DTG</td>
<td>35</td>
</tr>
<tr>
<td>Melanoma (A375)</td>
<td>Pentazocine, DTG (+/- dextrallorphan)</td>
<td>32</td>
</tr>
</tbody>
</table>
increases in ceramide with concomitant decreases in sphingomyelin (57).

Possible Mechanisms of \( \sigma \) Receptor Signal Transduction and Relevance to Cancer Cell Biology. Although there is considerable evidence for the involvement of \( \sigma \) receptors in cancer cell biology, the mechanism(s) through which these effects occur has not fully been discerned. \( \sigma \) receptors have been implicated in a wide range of functions, and formulating a unifying hypothesis for the molecular physiology of \( \sigma \) receptors to account for all of the varied functions will be a great challenge. Few reports exist that deal directly with the modes of action of \( \sigma \) receptors. The homology between the \( \sigma 1 \) receptor and the sterol isomerase (ERG2) of yeast is interesting, given that both the \( \sigma 1 \) receptor and the sterol isomerase have high affinity for \( \sigma 1 \) ligands. However, the \( \sigma 1 \) receptor has never been demonstrated to possess sterol isomerase activity. On the other hand, emopamil-binding protein, which also binds \( \sigma 1 \) ligands, was found to complement a yeast strain containing a deletion of the ERG2 gene and is a sterol isomerase like ERG2 (58).

Modulation of Ion Channels. Studies on the modulation of ion channels by \( \sigma 1 \) receptors have made advances in deducing the nature of the signal transduction mechanism (59). It has been suggested, despite the lack of homology between the \( \sigma 1 \) receptor and classic G-protein coupled receptors, that \( \sigma 1 \) receptors use G-proteins (60, 61). Accordingly, the \( \sigma 1 \) receptor could interact functionally with G-proteins through a mechanism that differs from that of classical G-protein-coupled receptors (59). However, most physiological experiments suggest that \( \sigma 1 \) receptor signal transduction does not involve any G-protein. Morio et al. (62) showed that the inhibition of K\(^+\) channels by \( \sigma \) drugs in NC-2B cells was not affected by pre-treatment with A23187, forskolin, phorbol-12,13-dibutyrate, cholera toxin, or pertussis toxin. These results are consistent with the well-known intracellular secondary messenger systems not being essential for the modulation of voltage-gated K\(^+\) channels by \( \sigma 1 \) receptors.

In rat sympathetic and parasympathetic neurons, \( \sigma \) receptors were shown to modulate high-voltage-activated Ca\(^{2+}\) channels including N-, L, P/Q- and R-type Ca\(^{2+}\) channels (63). Although \( \alpha 2 \)-selective drugs were not used, the rank order potency observed, haloperidol > ibogaine > (+)-pentazocine > DTG would suggest that this effect may be mediated by \( \alpha 2 \) receptors. In addition to reducing the peak amplitude of the Ca\(^{2+}\) current, \( \sigma \) receptors altered the kinetic properties of these channels. These data also suggested that neither a diffusible cytosolic second messenger nor a G-protein was involved.

Experiments on rat neurohypophysis also produced negative results for secondary messenger or G-protein mediation of \( \sigma 1 \)-receptor signaling (64). Modulation of K\(^+\) channels by pentazocine or SKF10047 persisted although nerve terminals were internally perfused with GTP-free solutions, the G-protein inhibitor GDP\(\beta\)S, or the G-protein activator GTP\(\gamma\)S. In DMS-114 cells (a tumor cell line isolated from a small-cell lung carcinoma), perfusion with GDP\(\beta\)S also failed to alter the response to SKF10047 (65). Similar negative results were obtained in tests for protein kinase involvement. Internal perfusion of nerve terminals with the non-hydrolysable ATP analog AMP\(\gamma\)P\(\gamma\)P had no effect on K\(^+\) current inhibition by \( \sigma 1 \) receptor drugs. Of particular significance was the observation that K\(^+\) channels present in excised outside-out patches were modulated by SKF10047 (64, 65). This effect excluded a role for any soluble cytoplasmic factor. In contrast, K\(^+\) channels present in cell-attached patches were not modulated by \( \sigma \) drug applied outside the patch, indicating that \( \sigma 1 \) receptors and the K\(^+\) channels under investigation must be in close proximity for any functional interaction to occur (64). Aydar et al. (20) reconstituted \( \sigma 1 \) receptor modulation of Kv 1.4 and Kv 1.5 channels in oocytes by heterologous expression of the K\(^+\) channels with \( \sigma 1 \) receptors. The modulation of ion channels in Xenopus oocytes was observed in the presence or absence of \( \sigma 1 \) drugs, suggesting that the \( \sigma 1 \) receptor may form a functional complex with the expressed ion channels (20). Indeed, these authors went on to show that the \( \sigma 1 \) receptor forms an immunoprecipitating complex with ion channels both in rat neurohypophysis and when coexpressed in Xenopus oocytes (20). In summary, studies on \( \sigma 1 \) receptor modulation of K\(^+\) channels, to date, have deduced the signal transduction mechanism of \( \sigma 1 \) receptors (a) to be membrane delimited (64, 65); (b) to be independent of G-protein coupling and protein phosphorylation (63–65); (c) to be reconstitutible in a heterologous system (20); (d) not to require cytoplasmic factors (64); and (e) to necessitate the \( \sigma 1 \) receptor and the K\(^+\) channel to be in close proximity (64), probably to form a stable macro-molecular complex (20).

Additional studies are required to determine whether the \( \sigma 1 \) receptor modulation of K\(^+\) channels is through a direct protein–protein interaction or through intermediate signaling molecule(s). Given the wide variety of functions that the \( \sigma 1 \) receptor are reported to serve, we

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**Table 3 Sigma receptor ligands as diagnostic agents in cancer**

<table>
<thead>
<tr>
<th>Drug</th>
<th>( \sigma 1 ) affinity ( K_c (\text{nm}) )</th>
<th>( \sigma 2 ) affinity ( K_c (\text{nm}) )</th>
<th>Subtype specificity</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[99mTc] oxotechnetium (V) complexes of amine-amide-dithiol</td>
<td>7.8 - 26</td>
<td>0.18 - 2.3</td>
<td>( \sigma 1 ) ( \sigma 2 )</td>
<td>39</td>
</tr>
<tr>
<td>[99mTc] {[({N-2-({N-propyl})-3,3-aza-bicyclononan-3a-yl}){2-{methoxy-5-methyl-phenylicarbamate}}mercaptopentyle{saminol}acetetyl}}-2-aminoetheresterolate</td>
<td>2,723</td>
<td>22</td>
<td>( \sigma 2 )</td>
<td>44</td>
</tr>
<tr>
<td>( N{4{fluorobenzyl}-4{3{bromophenyl}}acetamide}</td>
<td>3.6</td>
<td>667</td>
<td>( \sigma 1 )</td>
<td>97</td>
</tr>
<tr>
<td>( N{2{N{benzylpiperidin-4-yl}-4{yl}}</td>
<td>3.39</td>
<td>406</td>
<td>( \sigma 1 )</td>
<td>45</td>
</tr>
<tr>
<td>2{{1{7}}N{N{benzylpiperidin-4-yl}-2{iodobenzamide}</td>
<td>1.64</td>
<td>26.9</td>
<td>( \sigma 1 ) ( \sigma 2 )</td>
<td>50</td>
</tr>
<tr>
<td>( N{4{benzylpiperidin-4-yl}phenylacetamide}</td>
<td>3.9</td>
<td>240</td>
<td>( \sigma 1 )</td>
<td>98</td>
</tr>
<tr>
<td>( N{2{1{piperidiny{ethyl}}-3{iodo{1{7}}}4{methoxybenzamide}</td>
<td>11.82</td>
<td>208</td>
<td>( \sigma 1 ) ( \sigma 2 )</td>
<td>46, 51</td>
</tr>
<tr>
<td>( 4{{1{7}}iodo{2{1}} {piperidiny{ethyl}}benzensulfonamide}</td>
<td>1.6</td>
<td>1.66</td>
<td>( \sigma 1 ) ( \sigma 2 )</td>
<td>50</td>
</tr>
<tr>
<td>( 125{I} {N{N{benzylpiperidin-4-yl}-4{yl}}iodobenzamide}</td>
<td>1.7</td>
<td>25.2</td>
<td>( \sigma 1 ) ( \sigma 2 )</td>
<td>49</td>
</tr>
<tr>
<td>( 18{F} {N{N{benzylpiperidin-4-yl}-4{yl}}iodobenzamide}</td>
<td>2.1</td>
<td>8.1</td>
<td>( \sigma 1 ) ( \sigma 2 )</td>
<td>52</td>
</tr>
<tr>
<td>( N{4{fluorobenzyl}-4{3{bromophenyl}}acetamide}</td>
<td>1.2</td>
<td>6.1</td>
<td>( \sigma 1 ) ( \sigma 2 )</td>
<td>99</td>
</tr>
<tr>
<td>Series of benzamide analogs</td>
<td>15–12,900</td>
<td>8–716</td>
<td>Various</td>
<td>100</td>
</tr>
</tbody>
</table>

* Combined \( \sigma 1 \)-\( \sigma 2 \) binding.
favor a σ1 receptor signaling mechanism involving one or more intermediate signaling molecules (which are localized at or in the plasma membrane) rather than a direct interaction. Furthermore, the amino acid residues in Kv ion channels, involved in this interaction (direct or indirect) with σ1 receptors have not yet been determined. Elucidation of these issues would shed further light on the mechanism of σ1 receptor signaling.

Ion channels are expressed in cell lines derived from several different cancer types and can play an important role in metastasis, an integral aspect of which is the control of cell growth and proliferation (66). The dual observation that σ receptor expression is increased in tumor cell lines/tissues, and that σ1 receptors act as secondary subunits for some ion channels, is interesting, given the accumulating evidence for the involvement of different types of ion channels in proliferation (66) and metastatic activities of cancer cells (67–70). Because down-regulation of K+ channel amplitude has been associated with the metastatic phenotype in human prostate and breast cancer (71, 72), such an effect could underlie the proposed association between cancer progression and σ receptor drugs. As well as proliferation (72–74), there are several different ways in which ion channel activity may contribute to the cancer cell behavior, including migration (75), apoptosis (76), adhesion, and cytoskeletal organization (77–79) and secretion (80). It remains to be determined whether ion channels other than Kv’s, including those with a proposed role in the metastatic cascade, such as the voltage-gated Na+ channel (68, 81–84), are also modulated by σ drugs and, if so, whether this could relate to the cancer process.

Modulation of Ankyrin. Hayashi & Su (26) suggest that σ1 receptors may play a role in controlling the functioning of cytoskeletal proteins. Using immunocytochemical techniques, they showed that the σ1 receptor, ankyrin B and IP3R-3 are co-localized in perinuclear areas and areas of cell-to-cell communication, and proposed that this trimeric complex may regulate Ca2+ signaling (26). Although the exact underlying molecular mechanism has not yet been described, it is well known that adhesion and cytoskeletal organization are important factors in cancer cell biology (85, 86).

Modulation of Intracellular Ca2+. Vilner and Bowen (87) provided evidence that σ receptors in neuroblastoma cells may use Ca2+ signals to produce cellular effects. By using σ-active (but structurally similar) drugs, σ2-selective agents such as CB-64D, and σ1-selective agents it was shown that a fast and transient release of Ca2+ from the endoplasmic reticulum was induced specifically by the action of the σ2 receptor. In turn, intracellular Ca2+ modulation can affect protein kinase C activity. Indeed, in rat brain synaptosomes, dopamine transporter activity was found to be modulated by σ2 drugs via activation of protein kinase C (88). Because intracellular Ca2+ signaling is broadly important for many cellular processes, this may be an important mechanism through which σ2 drugs produce their documented effects on cancer cells.

Modulation of Sphingolipid Levels. Sphingolipid levels in MCF-7/Adr- and T47D breast tumor cell lines were investigated after application of σ2 specific agonists to further understand the molecular mechanism by which σ2 drugs could cause their observed morphological and apoptotic effects in various cancer cell lines (57). CB-184 caused a dose-dependent increase in ceramide levels and concomitant decrease in sphingomyelin within the MCF-7/Adr− and T47D breast tumor cell lines. These effects were attenuated by N-phenethylpiridone, a nonspecific σ-receptor antagonist. These results suggested that σ2 receptors may use sphingolipid products to affect Ca2+ signaling, cell proliferation, and survival (57).

Conclusions and Future Perspectives

In conclusion, the σ receptors play a role in a multitude of cellular functions and also manifest themselves pathologically. The involvement of σ receptors in the cellular pathophysiology of cancer is apparent from the high density of σ1 and σ2 binding sites found in various tumor cell lines and tissues. Consequently, σ drugs have been suggested to be potentially useful tumor imaging agents. The ability of σ2 drugs to inhibit tumor cell proliferation through mechanisms that may involve apoptosis, intracellular Ca2+, and sphingolipids have been investigated, and such findings may lead to the development of σ drugs as cancer therapeutic agents. It is possible that an increase in σ2 receptor expression is a significant event in transition from normal to malignant cells, although additional detailed studies are required to confirm the available data. Importantly, metastasis is a multistep process of which cellular proliferation is but one facet. Further research would be interesting to determine whether σ receptors are involved in other metastatic cell behaviors such as adhesion, secretion, motility, and invasion. The proposed molecular model of the σ1 receptors (Fig. 1) should be valuable to the understanding of the cellular functions of σ1 receptors and could ultimately facilitate the determination of the molecular basis of the σ2 receptor. The nature of the endogenous ligand(s) for σ receptors is also an important question and awaits clarification. It is highly possible that the σ receptors are not “classic” ligand-gated receptors. It is tempting to speculate that σ receptors could be auxiliary subunits for target proteins involved in various cellular functions as shown for Kv channels (20).

An ultimate challenge for research in this field is to produce a unified model describing the molecular mechanisms of σ receptors that can encompass the known biological and pathophysiological role. Only through a detailed molecular investigation of σ receptor action will we be able to understand the involvement of σ receptors in cancer biology and possibly design or discover new σ receptor agents that can be used as effective diagnostic and/or therapeutic agents in cancer management.

References

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25. Hayashi T, Su TP. Sigma-1 receptors (sigma (1) binding sites) form raft-like microdomains and target lipid droplets on the endoplasmic reticulum: roles in endoplasmic reticulum lipid compartmentalization and export. J Pharmacol Exp Ther 2003;306:718–25.

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Sigma Receptors and Cancer: Possible Involvement of Ion Channels

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