Introduction to Sigma Proteins: Evolution of the Concept of Sigma Receptors

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Contents

Abstract

For over 40 years, scientists have endeavored to understand the so-called sigma receptors. During this time, the concept of sigma receptors has continuously and significantly evolved. With thousands of publications on the subject, these proteins have been implicated in various diseases, disorders, and physiological processes. Nevertheless, we are just beginning to understand what sigma proteins do and how they work. Two subtypes have been identified, Sigma1 and Sigma2. Whereas Sigma1 (also known as sigma-1 receptor, Sig1R, σ1 receptor, and several other names) was cloned over 20 years ago, Sigma2 (sigma-2 receptor, σ2 receptor) was cloned very recently and had remained a pharmacologically defined entity. In this volume, we will focus primarily on Sigma1. We will highlight

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several key subject areas in which Sigma1 has been well characterized as well as (re)emerging areas of interest. Despite the large number of publications regarding Sigma1, several fundamental questions remain unanswered or only partially answered. Most of what we know about Sigma1 comes from pharmacological studies; however, a clearly defined molecular mechanism of action remains elusive. One concept has become clear; Sigma1 is not a traditional receptor. Sigma1 is now considered a unique pharmacologically regulated integral membrane chaperone or scaffolding protein. A number of landmark discoveries over the past decade have begun to reshape the concept of sigma receptors. With the rapid emergence of new information, development of new tools, and changing conceptual frameworks, the field is poised for a period of accelerated progress.

Keywords

Alcohol abuse • Allosteric modulation • Anchor patch • Cancer • Chaperone • Crystal structure • Drug addiction • Drug mechanism of action • Imaging agents • Medicinal chemistry • Neurodegeneration • Neuronal excitability • Nuclear magnetic resonance • Pain • Pharmacology • Puzzle • Scaffold • Self-administration • Sigma1 • Sigma-1 receptor • Sigma2 • Sigma-2 receptor • Small molecule modulator • Three-dimensional homology model

1   Historical Perspective

The concept of sigma receptors has continually evolved for over four decades. While most in the field agree that they are important, there is little agreement on anything else. Even the nomenclature to describe the binding sites varies. In the literature, one will find: σ_1 receptor, σ1R, σ_2 receptor, sigma1 receptor, sigma2 receptor, sigma-1 receptor, sigma-2 receptor, $sigma_1$ receptor, $sigma_2$ receptor, Sig-1R, Sigma-R1, SigmaR1, Sigmar1, ALS16, AAG8, and Sigma1 (which is our preferred nomenclature for this subtype, to indicate that this unique protein is not a traditional receptor).

The story has undergone many twists and turns, and every decade since its original identification, major new developments and discoveries have attempted to redefine the field. Originally identified in 1976, Martin and colleagues proposed three distinct opioid receptor classes, mu, kappa, and sigma, based upon behavioral studies using morphine, ketocyclazocine, and the benzomorphan SKF10047. They noted that the opioid antagonist naltrexone antagonized them all, leading to the identification of sigma as an opioid receptor (Martin et al. 1976). In the original study, the SKF10047 stereoisomer used was not described; however, subsequent investigators used (+)-SKF10047 to define sigma binding sites and identified them as receptors that clearly were not opioid (Su 1982). Since then, a large number of chemically diverse compounds that have affinity for sigma receptors have been reported (reviewed in the chapter by Weber and Wunsch in this volume and more broadly reviewed, collectively in Cobos et al. 2008; Maurice and Su 2009; Narayanan et al. 2011). As more compounds with affinity for sigma binding sites became

available, the putative sigma receptors were subdivided into two categories: Sigma1 and Sigma2 based primarily on ligand binding studies (Hellewell and Bowen 1990).

The cloning of Sigma1 (Hanner et al. 1996) was a major milestone in the field. It revealed that Sigma1 was unlike any traditional receptor; indeed, it later became clear that Sigma1 shares no significant homology with any other protein encoded in the human genome. As the field advanced through the end of the twentieth and into the twenty-first century, although the label "receptor" continued (and continues) to be used, it became increasingly clear that Sigma1 does not fit the traditional definition of a receptor. In 2007, the notion that Sigma1 is not a receptor, but rather, a chaperone protein was introduced (Hayashi and Su 2007), and the notion that Sigma1 functions as an oligomeric structure was introduced in 2014 (Gromek et al. 2014). A three-dimensional (3-D) homology model was developed in 2011 (Laurini et al. 2011) and a solution phase structure was established by nuclear magnetic resonance (NMR) in 2015 (Ortega-Roldan et al. 2015). In 2016, the first crystal structure of Sigma1 was resolved (Schmidt et al. 2016). Very recently Alon and colleagues published the cloning of Sigma2 (Alon et al. 2017; Kim and Pasternak 2017). The crystal structure of Sigma2 is surely not far behind.

Functional studies in rodent models of behavior and in vitro cell based assays have implicated both subtypes of sigma receptor in a range of physiological and pathophysiological contexts: neurodegenerative diseases, neuronal plasticity, neuronal development, cognition, memory, learning, various types of pain, cancer, immune modulation, and many others. However, despite more than 4,000 publications on the subject over four decades, fundamental questions regarding what sigma proteins do in each context and how they work are unanswered or partially answered. This historical overview does not cover the hundreds of important discoveries and nuances of the twists and turns underlying the evolution of the field. A detailed and comprehensive history of sigma proteins would require multiple volumes from diverse perspectives. This volume will focus primarily on the literature regarding Sigma1 and will provide insights into the state of the field through a number of key examples.

2   Objectives of this Volume

So, what is the state of the field? The analogy of a puzzle comes to mind, and we see the more than 4,000 publications representing pieces of a complex jigsaw puzzle. Thus, our goal is to identify "anchor patches" of the Sigma1 puzzle, that is, key related findings that provide disproportionate insight into the structure and function of Sigma1 (concept of "anchor patches" reviewed in Cho et al. 2010). These include our current understanding of: Sigma1 structural biology; Sigma1 pharmacology; Sigma1 in neurodegeneration and neuronal plasticity; Sigma1 in cancer and its ligands in the context of cancer; Sigma protein radiotracers and imaging agents; Sigma1 in pain; Sigma1 ligands as non-opioid antinociceptive agents; and Sigma1 in drug abuse and addiction. This introduction to the volume *Sigma Proteins:*

Evolution of the Concept of Sigma Receptors provides a brief overview of the chapters that address some of the "anchor patches" to the sigma puzzle.

3   Insights into the Structure of Sigma1

For decades, sigma proteins have remained enigmatic binding sites, largely defined by the pharmacology of small molecule ligands. Recently, important advances have been made, which provide significant insight into our understanding of the structure and functionality of Sigma1. Perhaps the most exciting recent development has been the publication of the crystal structure of Sigma1 (Schmidt et al. 2016; Kruse 2016). The chapter by Kruse and colleagues entitled *Structural Insights into Sigma1 Function* discusses their Sigma1 crystallographic studies and the technological innovations that enabled this landmark discovery. They propose that the crystal structure provides a framework to understand the published mutagenesis data and the diverse molecular pharmacology of Sigma1 ligands (Kruse 2016). The crystal structure shows a high resolution but static snapshot of Sigma1. With this information now available, it will be fascinating to investigate and elucidate the differential dynamic effects of Sigma1 antagonists/inhibitors, agonists/activators, and membrane lipids/cholesterols on its conformation and subsequent modulation of Sigma1 associated proteins. The development of nuclear magnetic resonance (NMR) approaches and in silico tools to analyze the structural biology and pharmacology of Sigma1 represents another major advance in the field. The *3-D homology model of Sigma1 receptor* chapter by Pricl and colleagues proposes a three-dimensional (3-D) model of Sigma1 generated from homology modeling techniques, and proposes how this approach can be applied as a docking model-based virtual drug screen for rational ligand design (Laurini et al. 2017).

Interestingly, the crystal structure and 3-D homology models do not match. For example, whereas previous biochemical studies proposed a two-transmembrane domain topology, the crystal structure shows a single transmembrane domain protein with a short ER-lumenal peptide and one relatively large cytoplasmic domain containing a cupin-like ligand-binding barrel (Schmidt et al. 2016; Kruse 2016). According to Pricl, this discrepancy raises a critical question: which is the true structure of Sigma1, the NMR solution-solved and in silico derived 3-D homology model or the X-ray-solved crystal structure? How can the differences between the two structures be explained? Pricl and colleagues propose that the Sigma1 protein may adopt different structures under solid (revealed by the crystal structure) and solution (revealed by the in silico and NMR models) states. Ultimately, Pricl and colleagues argue that the field still has a long way to go before it is able to provide an unequivocal answer to these questions. Resolution of these discrepancies and advances in our understanding of Sigma1 structure will position the field for new discoveries as well as re-evaluation of older data and models.

4   Development of Sigma1 Medicinal Chemistry

Perhaps one of the most daunting tasks in producing this volume was to provide clarity and coherence to the vast, diverse, and complex field of Sigma1 medicinal chemistry. Weber and Wunsch accept this challenge in their chapter entitled *Medicinal Chemistry of Sigma1 (σ_1) Receptor Ligands: Pharmacophore Models, Synthesis, Structure Affinity Relationships*, *and Pharmacological Approaches* (Weber and Wunsch 2017). This chapter comprises two principal parts: (1) review of the various pharmacophore models for Sigma1 ligands and the role of the 3-D homology model and the crystal structure in future development; (2) the synthesis and biological properties of nine prototypic Sigma1 ligands. In addition to experimentally determined ligand binding affinity and molecular dynamics simulations based on a 3-D homology model, the authors present the following published data as readouts of biological properties: cancer cell growth and survival inhibition and apoptosis, neurite outgrowth in vitro, and data from pain behavioral assays. The authors also review the discovery and development of Sigma1 ligands as radiotracers for positron emission tomography (PET) and imaging agents, including an agent that is in clinical trials for central nervous system (CNS) imaging of patients suffering from major depression.

During the past decade, considerable progress has been made, and Weber and Wunsch present an encouraging outlook for the evolution of Sigma1 medicinal chemistry in light of recent structural discoveries as well as the advancement of a Sigma1 ligand, S1RA, through clinical trials for neuropathic pain (also discussed in the chapters by Vela and colleagues (Merlos et al. 2017)).

5   Sigma1 Pharmacology in Neurodegeneration and Neuronal Excitability

The vast majority of the Sigma1 literature addresses aspects of neuropharmacology. In their chapter *Sigma1 (σ_1) Receptor in Memory and Neurodegenerative Diseases*, Maurice and Goguadze review and discuss pharmacologic and genetic evidence of Sigma1 involvement in learning and memory disorders, cognitive impairment, and neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, and Huntington's disease (Maurice and Goguadze 2017). They review a number of recent publications that highlight the efficacy of drugs with affinity for Sigma1 in mitigating symptoms associated with neurodegenerative disorders in preclinical rodent models. They also point out that compounds with affinity for Sigma1 are in clinical trials, and that one Sigma1 drug is in phase II clinical trials for Alzheimer's disease (Maurice and Goguadze 2017).

Sigma1 in neuronal signaling and regulation of ion channels is reviewed in the chapter by Kourrich entitled *Ion Channels and Neuronal Excitability* (Kourrich 2017). In this chapter, Kourrich describes and discusses Sigma1 dependent modulation of voltage gated ion channels (VGICs) and ligand gated ion channels (LGICs). He describes the range of proteins with which Sigma1 has been reported

to interact and proposes this as the reason for the plethora of neuronal functions in which Sigma1 has been implicated. Kourrich proposes that Sigma1 is an integral membrane protein at the plasma membrane, with extracellular N- and C-termini that regulates VGIC conductance at the cell surface, and proposes that Sigma1 is an atypical auxiliary regulatory subunit for ion channels for VGICs. He discusses the potential mechanisms to explain observed effects of Sigma1-associated activities on intrinsic and synaptic excitability, and how these mechanisms affect overall neuronal activity.

6   Sigma1 as a Drug Target for Pain

As Vela and colleagues emphasize in their chapter, *Sigma-1 Receptor and Pain*, there is a critical need for new potent and efficacious non-opioid analgesics or agents that increase the potency and efficacy of opioids in order to diminish or bypass their addictive properties and other serious, unwanted side effects (Merlos et al. 2017).

The authors review the literature as well as their own studies demonstrating the roles of Sigma1 in nociception. They discuss the pain-attenuated phenotype of the published *SIGMAR1* knockout mouse and the antinociceptive properties of Sigma1 putative antagonists/inhibitors in pain of varied etiology, including neuropathic, inflammatory, ischemic, visceral, and postoperative pain. They review the proposed mechanisms by which Sigma1 antagonists/inhibitors elicit antinociceptive effects in peripheral as well as central nervous system (central) pain. They propose that unlike opioids, Sigma1 antagonists/inhibitors do not alter normal sensory perception or mechanical and thermal sensitivity thresholds in normal animals but only exert antihyperalgesic and antiallodynic effects specifically under sensitizing or pathophysiological conditions such as chronic pain. The authors point out that Sigma1 antagonists/inhibitors are thus not analgesics, as strictly defined, but rather antiallodynic and antihyperalgesic agents.

Finally, Vela and colleagues highlight and describe in detail S1RA (also known as E-52862), an investigational Sigma1 antagonists/inhibitors currently in phase II clinical trials for chronic neuropathic pain and postoperative pain in combination with morphine. Clearly, the outcome of these clinical trials is of considerable interest to the field as it will confirm the potential of this new target, drug class, and approach to pain management.

Sigma1 has been associated with myriad signaling and transduction systems over the decades. Evidence over the past 20 years has demonstrated that Sigma1 ligands can modulate opioid analgesia in vivo and opioid receptor signaling mechanisms in vitro. In his chapter entitled *Allosteric Modulation of Opioid G-Protein Coupled Receptors by Sigma₁ Receptors*, Pasternak describes how Sigma1 ligands can function as allosteric modulators of G-protein coupled receptors (GPCR) function through their association with the Sigma1 (Pasternak 2017). He reviews the literature for evidence of the signal modulatory role of

Sigma1 on GPCR activity in various regions of the CNS and argues that the general actions of Sigma1 extend beyond its putative chaperone actions.

Sigma1 antagonist/inhibitor potentiation of opioid analgesia highlights their potential use in combination with opioids, as opioid adjuvants, to selectively enhance analgesic effects while minimizing the dose of opioids, thus reducing side effects and potential for addiction and increasing the safety margin of opioid treatments. These data along with the antinociceptive properties of S1RA alone represent a promising new approach to safely treat intractable chronic pain conditions. Emergence of Sigma1 ligands as novel, non-opioid pain relief agent is timely indeed, in light of the current opioid epidemic in the USA.

7   Alcohol and Drug Abuse and Addiction

Sigma proteins, both Sigma1 and Sigma2, historically have been described as modulators of the effects of psychomotor stimulants, such as cocaine and methamphetamine, and have been proposed as agents to mitigate stimulant drug abuse. However, the published results have been varied and the pharmacological mechanisms underlying these effects remain unclear. Katz and colleagues in their chapter, *A Role for Sigma Receptors in Stimulant Self-Administration and Addiction*, review the effects of sigma receptor ligands (both putative agonists/activators and antagonists/inhibitors) in three relevant pharmacological assays of rodent behavior: stimulant discrimination, place-conditioning, and self-administration (Katz et al. 2017). The literature suggests that Sigma1 agonists/activators generally substitute for psychomotor stimulants in the discrimination assay, and Sigma1 antagonists/inhibitors generally block stimulant effects in the place-conditioning assay. However, the responses are more complex and do not necessarily follow these general trends, and appear to be condition and context dependent. Interestingly, test subjects self-administered Sigma1 agonists/activators only after stimulant self-administration, suggesting that psychostimulants modify the status of Sigma1 in a manner that creates independent reinforcement mechanisms. The authors observe that selective Sigma1 antagonists/inhibitors do not block stimulant self-administration; however, nonselective Sigma1 antagonists/inhibitors that also bind the dopamine transporter can decrease stimulant self-administration. Thus, they propose that concomitant targeting of both dopaminergic and sigma receptors selectively suppresses mechanisms involved in stimulant abuse and reveal the possibility of new drug combination strategies to prevent stimulant abuse.

Whereas extensive research has been performed regarding the neurobiological mechanisms underlying alcohol addiction, pharmacological intervention in alcohol abuse disorders remains limited and ultimately ineffective. In the chapter *Sigma Receptors and Alcohol Use Disorders*, Sabino and Cottone review emerging evidence suggesting that Sigma1 plays a role in the rewarding and reinforcing effects of alcohol, and that Sigma1 may be a novel target for the pharmacological treatment of alcohol use disorders (Sabino and Cottone 2016). This work builds upon established literature implicating Sigma1 in psychostimulant pharmacology. The

authors review the literature describing the efficacy of Sigma1 antagonists/ inhibitors in reducing excessive alcohol drinking and alcohol-seeking behavior in several animal models.

8   Sigma1 Pharmacology in the Context of Cancer

Most of the literature regarding Sigma1 describes it in the context of neuropharmacology; however, a number of publications over the years have suggested a role for Sigma1 in tumor biology. Although there is currently no clinically used anticancer drug that targets Sigma1, a growing body of evidence supports the potential of Sigma1 ligands as cancer therapeutic agents with a range of beneficial activities. Indeed, in preclinical models, compounds with affinity for Sigma1 have been reported to inhibit cancer cell proliferation and survival, tumor growth, cell adhesion and migration, to alleviate cancer-associated pain, and to have immunomodulatory properties. In their chapter *Sigma1 Pharmacology in the Context of Cancer*, Kim and Maher review and discuss the status of Sigma1 in cancer (Kim and Maher 2017).

The authors point out that although the literature supports a potential role for Sigma1 in cancer, fundamental questions regarding the pharmacological mechanism of action of Sigma1 ligands and the physiological relevance of aberrant *SIGMAR1* transcript and Sigma1 protein expression in certain cancers remain unanswered or only partially answered. For example, there is no compelling evidence that *SIGMAR1* is an oncogene or that Sigma1 is an oncogenic driver protein; however, several studies have demonstrated that cancer cells require functional, intact Sigma1 to grow, proliferate, and survive. Kim and Maher propose and provide preliminary direct and indirect evidence in support of the hypothesis that Sigma1 is a component of the cancer cell support machinery promoting protein and lipid homeostasis, that it facilitates protein interaction networks, and that it allosterically modulates the activity of its associated proteins. The authors propose that Sigma1 ligands may be allosteric modulators of protein–protein interactions. This is consistent with the prevailing but unclearly defined notion that Sigma1 itself is devoid of intrinsic signaling or enzymatic activity, rather it acts as a modulator of the intracellular signaling and activities of other receptor systems. However, the biochemical mechanism by which Sigma1 elicits these effects remains unclear. Recent developments in Sigma1 structural biology should facilitate progress in this domain.

9   Sigma2 as a Target for Imaging Agents

Mach and colleagues review Sigma2 ligands as imaging tools in their chapter *Molecular Probes for Imaging the Sigma-2 Receptor:* In Vitro *and* In Vivo *Imaging Studies* (Zeng et al. 2017). The sigma-2 (σ_2) receptor or Sigma2 has been a pharmacologically defined entity for decades. Interestingly, studies with

radiolabeled probes have demonstrated that the level of Sigma2 binding sites correlates with the proliferative status of solid tumors (Wheeler et al. 2000). Thus, small molecule radiotracers with affinity and selectivity for Sigma2 have been evaluated in preclinical and more recently in clinical trials to assess the proliferative status of human tumors by positron emission tomography (PET) (Zeng et al. 2017). Of note, the authors describe the development and promising results from preliminary clinical imaging studies with [^{18}F]ISO-1, a Sigma2 probe, in cancer patients.

The true utility of imaging Sigma2 in solid tumors as a diagnostic and/or predictive biomarker of therapeutic response will depend on a clearer understanding of what has remained an enigmatic pharmacological binding site until very recently. Since the writing of this volume, Sigma2 has been cloned and identified as transmembrane protein 97 (TMEM97), a relatively poorly understood integral membrane protein implicated in cholesterol metabolism (Alon et al. 2017; Kim and Pasternak 2017; Bartz et al. 2009). With the cloning of Sigma2/TMEM97, the compounds, radiotracers, and fluorescent probes developed for Sigma2 over the decades now have a biochemically defined target for pharmacological mechanism of action studies. And the field is poised to open another interesting new avenue of research.

10   Outlook

The sigma proteins have been primarily defined by the activities regulated by their ligands. In the case of Sigma1, it has no clearly defined signaling or enzymatic activity, and the pharmacology of Sigma1 ligands has been defined by the proteins with which it interacts. The myriad, context dependent effects of Sigma1 ligands present a complex picture. There is still much to be done to define unifying mechanisms of action of Sigma1 ligands. A fundamentally important question is what are the structural changes that define Sigma1 agonists/activators and antagonists/inhibitors, as these putative pharmacological activities have remained undefined at the molecular level. The structural insights and tools that have recently emerged will be instrumental in answering fundamental questions regarding how these proteins work, how ligands modulate their activity, and will accelerate drug discovery in this field.

The concept of the sigma receptor has evolved significantly over the past 40 years. Along the way, thousands of publications on the subject have provided key pieces to the sigma puzzle, and the field is in its best position yet to connect the puzzle pieces and to establish a clearer picture of the sigma proteins, how they work, and to explain their role in the diverse physiological and pathophysiological processes in which these proteins have been implicated.

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