The Sigma Enigma: Can Sigma Receptors Provide a Novel Target for Disorders of Mood and Cognition?

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Issue: *Evidence currently suggests that σ_1 and σ_2 receptors both mediate important functional and behavioral actions in the central nervous system and serve as novel targets for treatment of depression, cognitive disorders, cocaine abuse, and stroke.*

Sigma receptors are provocative, mysterious, and controversial targets of many psychotropic drugs and are only now beginning to be understood. Sigma receptors are not a type of opiate receptor nor a type of receptor on the NMDA (*N*-methyl-D-aspartate) glutamate receptor complex, but they are now known to be a unique set of proteins with at least 2 subtypes of receptors: σ_1 and σ_2.[1,2]

Structure and Function of Sigma Receptors

Sigma receptors are located in many tissues where they represent sites in the endoplasmic reticulum (ER), not in cell membranes.[1–3] They are thought to be key regulators of intracellular calcium signaling; however, σ_1 and σ_2 receptors are found in different locations throughout the brain, the functional significance of which is still under investigation.[1,2]

The σ_1 receptor is a 223–amino acid protein with 2 transmembrane domains, one near the N-terminus and the other in the middle of the protein, with both the N- and C-terminus of the receptor localized in the lumen of the ER.[2,3] In the ER, the σ_1 receptor plays a key role in potentiating intracellular calcium mobilization, acting as a sensor/modulator of calcium signaling.[2,3] Occupancy of σ_1 receptors by agonists causes translocation of this receptor from the ER to the peripheral areas (membranes) of neurons, where σ_1 receptors may regulate ion channels and other neurotransmitter receptors,[2,3] and thus neurotransmitter release, including that of dopamine, glutamate, serotonin, norepinephrine, acetylcholine, and others.[1–3] Sigma receptors also regulate neurotrophic factor signaling, and activation of sigma receptors can cause robust antiapoptotic actions and promote neuronal differentiation, neurite sprouting, and myelination by oligodendrocytes.[1–3]

Although their structure and function is less understood than σ_1 receptors,[1,2] σ_2 receptors may be involved with the mechanism of action of cocaine, since cocaine binds to both types and σ_2 antagonists reduce drug use in animal models.[1]

Sigma Receptors and CNS Disorders

Sigma receptors are reportedly reduced in brains of patients with Alzheimer's disease (AD), Parkinson's disease, and schizophrenia.[1] Sigma-1 agonists enhance acetylcholine release and reverse anticholinergic amnesia in animals, suggesting possible utility as symptomatic treatment for AD or for other cognitive disorders,[1,2] and also improve spatial impairment of learning caused by NMDA receptor antagonists in animal models.[1–4] Specifically, fluvoxamine, an SSRI with σ_1 agonist properties (Table 2), improves PCP-induced cognitive impairment in mice,[4] which suggests possible utility of σ_1 agonists in cognitive disorders linked to aberrant glutamate neurotransmission, as postulated for major depression, bipolar depression, treatment-resistant depression, and schizophrenia.[5]

Animal behavioral models have demonstrated that selective σ_1 agonists, like neurosteroids, [1,7] have antidepressant,[1,6,7] antianxiety,[1,5] and anti-OCD actions.[1,5] Additionally, on the basis of animal models, we find σ_1 agonists may be neuroprotective and reduce neuronal damage in stroke, whereas σ_2 receptors may regulate movement disorders and drug abuse, especially cocaine.[1]

Sigma Receptors and Clinical Studies of Psychotropic Drugs

Several known psychotropic drugs have surprisingly turned out to have σ_1 agonist properties (Table 1),[1,2,6,8] and several antidepressants in particular have moderately high affinity for σ_1 sites (Table 2).[8] It is yet unknown whether this property contributes to

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Table 1. Agents in Clinical Use and Misuse With Actions on Sigma Receptors

Agonists	
Amantadine	Some TCAs
Cocaine	PCP (phencyclidine)
Dextromethorphan	Pentazocine
Fluvoxamine	Fluoxetine (weak)
Ketamine	Memantine (weak)
Antagonists	
Haloperidol	Sertraline (possible/unsure)

Table 2. Affinity of Various Antidepressants for Sigma Receptors

Agent	K_i (nM) σ_1	K_i (nM) σ_2	K_i Ratio σ_1/σ_2
Fluvoxamine	36	8,439	234
Sertraline	57	5,297	93
Fluoxetine	240	16,100	68
Citalopram	292	5,410	19
Imipramine	343	2,107	6
Paroxetine	11,893	22,870	12
Desipramine	1,987	11,430	6

any of the established therapeutic or nontherapeutic actions of the various drugs listed in Tables 1 and 2, since none of these agents is selective for σ_1 receptors, and each is better known for the other pharmacologic properties they exhibit. Nevertheless, there are hints from preclinical and early clinical studies that σ_1 agonist actions may contribute to antidepressant,[1,6–11] mood-stabilizing,[11] antipsychotic,[1,6,9,10,12] and procognitive actions[4,12] in patients with mood disorders.

One of the most interesting compounds is fluvoxamine, best known as an SSRI[5] but now shown to have high affinity for[5,6,8] and high occupancy of[13] σ_1 receptors (Table 2), which has been shown to have superior efficacy in delusional depression compared to antidepressants without this property (venlafaxine).[6,9] Even sertraline, a drug with only moderate affinity for σ_1 receptors[6,8] (Table 2), may have superior efficacy over paroxetine in delusional depression.[6,10] An add-on study of fluvoxamine to antipsychotics reports possible procognitive actions in schizophrenia,[12] consistent with its reversal of NMDA-antagonist–induced cognitive deficits in animals.[4] These results suggest that studies of σ_1 agonists like fluvoxamine could be interesting to conduct in patients with cognitive dysfunction due to disorders theoretically linked to glutamate dysfunction, such as treatment-resistant depression and bipolar depression. Lack of activation of psychosis or mania by monotherapy for delusional depression with fluvoxamine[6,9] or sertraline[6,10] also suggests a possible role in treating depressed mood in bipolar depression as well.

Supporting the notion that σ_1 receptor agonists may be useful in mood disorders is the observation that numerous other agents with activity at σ_1 receptors are also proving useful in mood disorders.[1,5,6,8,11] Thus, amantadine,[5,14] memantine,[5,14] ketamine,[5] and dextromethorphan[11] have σ_1 agonist properties in addition to their other pharmacologic properties and have all been reported to have some evidence of antidepressant efficacy in various small clinical reports.[1,5,11] Dextromethorphan, a weak NMDA antagonist with σ_1 properties,[5] is reported effective specifically in the treatment of labile affect associated with pseudobulbar states, sometimes also called involuntary emotional expression disorder,[11] suggesting a trial in other unstable mood disorders such as bipolar disorder may be informative.

These are early days in the investigation of sigma receptors as novel therapeutic targets in psychiatric disorders, but hopefully further research with more selective compounds will help to unravel the sigma enigma. ◆

Take-Home Points

1. Sigma receptors are present in many cells, from neurons to glia to many peripheral tissues.
2. Unlike neurotransmitter receptors located within presynaptic and postsynaptic neuronal membranes, sigma receptors are located in the endoplasmic reticulum where they play a key role in regulating intracellular calcium signaling.
3. Naturally occurring neurosteroids as well as many psychotropic drugs bind to sigma receptors; sigma receptors may thus mediate some actions of fluvoxamine, amantadine, dextromethorphan, cocaine, and phencyclidine (PCP).
4. Selective sigma agents hold promise as novel antidepressants and as drugs in the treatment of cognition, and possibly for drug abuse, for other conditions, and for potential neuroprotection.

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