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Sigma receptors: potential targets for a new class of antidepressant drug

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Abstract

Despite the widespread and devastating impact of depression on society, our current understanding of its pathogenesis is limited. Likewise, existing treatments are inadequate, providing relief to only a subset of people suffering from depression. The search for more effective antidepressant drugs includes the investigation of new molecular targets. Among them, current data suggests that sigma receptors are involved in multiple processes effecting antidepressant-like actions *in vivo* and *in vitro*. This review summarizes accumulated evidence supporting a role for sigma receptors in antidepressant effects and provides a conceptual framework for delineating their potential roles over the course of antidepressant treatment.

Keywords

Antidepressant; Glutamate; Serotonin; Sigma receptor; Signal transduction; Neuroplasticity; Neurogenesis

1. Introduction

Depression is one of the top ten causes of morbidity and mortality, afflicting up to 20% of the world's population (Nestler et al., 2002; Berton and Nestler, 2006). In addition to its social toll, the economic burden of depression contributes approximately $44 billion in lost productivity annually in the United States (Stewart, 2003). The symptoms of depression are chronic, recurring, and life threatening (Berton and Nestler, 2006). Unfortunately, our current understanding of the etiology of depression is still rudimentary and current pharmacotherapeutic options are far from ideal.

Antidepressant drugs were discovered serendipitously in the 1950s (Berton and Nestler, 2006). The first two antidepressant drugs in widespread clinical use, iproniazid, a monoamine oxidase inhibitor (MAOI) and imipramine, a tricyclic antidepressant (TCA),

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were originally prescribed for other indications, but were found to possess potent antidepressant effects in humans (Deverteuil and Lehmann, 1958; Ball and Kiloh, 1959). They were subsequently shown to enhance central serotonin or norepinephrine neurotransmission, suggesting that their antidepressant actions could be attributed to this effect and by extension that depression was due to deficiencies in monoamine neurotransmission (Chaput et al., 1991; Blier and Bouchard, 1994; Slattery et al., 2004). Accordingly, the monoamine hypothesis of depression was established and continues to maintain a dominant role in antidepressant drug development (Prange, 1964; Schildkraut, 1965). The late 1980s were marked by the introduction of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), which had a significantly reduced liability for unwanted side effects relative to the tricyclic antidepressants and MAOIs. Additional advances followed with the development of serotonin-norepinephrine reuptake inhibitors (SNRIs) and norepinephrine reuptake inhibitors (NRIs) which also produced antidepressant actions with fewer serious side effects than the classical tricyclic antidepressants and MAOIs. Despite these successes and the continued use of these medications, better therapeutic options are still needed (Slattery et al., 2004; Berton and Nestler, 2006; Racagni and Popoli, 2008; Lopez-Munoz and Alamo, 2009).

Major problems of existing antidepressant drugs include delayed clinical benefit, serious side effects, and a response in less than 50% of patients (Berton and Nestler, 2006). Consequently, there is still a great need for faster acting, safer, and more effective treatments for depression. In an effort to expand beyond classical monoamine based strategies, recent medication development activities have focused on neurotrophic factors, glutamatergic systems, the hypothalamic-pituitary axis (HPA) as well as a number of other less well characterized novel targets. Studies in these areas are ongoing and recent reviews are available on these topics (Castren and Rantamaki, 2008; Pariante and Lightman, 2008; Racagni and Popoli, 2008; Sen and Sanacora, 2008; aan het Rot et al., 2009). The present review focuses on another novel target for antidepressant therapeutic development, the sigma receptor.

In addition to the classical monoamines, and the more recently implicated novel receptor systems, sigma receptors have emerged as compelling targets for antidepressant drug development. Numerous *in vivo* studies indicate that sigma receptor agonists produce antidepressant-like effects in animals and humans (Matsuno et al., 1996; Ukai et al., 1998; Skuza and Rogoz, 2002; Skuza, 2003; Wang et al., 2007b). Further, many *in vitro* studies demonstrate that sigma receptor agonists modulate the activities of the same neurotransmitter systems, signaling pathways, and brain regions implicated in the pathophysiology of depression and the therapeutic effects of currently marketed therapeutics.

A number of excellent reviews have been published recently that provide updated accounts of sigma receptor pharmacology (Hashimoto and Ishiwata, 2006; Cobos et al., 2008; Maurice and Su, 2009; Tsai et al., 2009) or that specifically address the putative role of sigma receptors in neuropsychiatric disorders, including depression (Hayashi and Su, 2008; Stahl, 2008; Kulkarni and Dhir, 2009). This review focuses on sigma receptors as a potential target for the development of a new class of antidepressant drugs. The review begins with a

summary of evidence implicating sigma receptors in the actions of antidepressant drugs. It then provides a conceptual framework for potential mechanism(s) of action of sigma-active antidepressant drugs and an account of recent studies supporting this conceptual framework.

1. Sigma receptors

Sigma receptors were initially proposed as a subtype of opioid receptor (Martin et al., 1976). Later studies demonstrated that they are unique proteins highly conserved across species, cell types, and organelles (Hanner et al., 1996; Kekuda et al., 1996; Seth et al., 1997; Seth et al., 1998; Mei and Pasternak, 2001). Sigma receptors are widely distributed in the body (Wolfe et al., 1989; Harada et al., 1994; Hellewell et al., 1994; Novakova et al., 1995; Wolfe et al., 1997). In the brain, they are found in significant concentrations in limbic and endocrine areas that have been implicated in the pathophysiology of depression (Drevets et al., 2008; aan het Rot et al., 2009), including the hippocampus, frontal cortex, hypothalamus, and olfactory bulb (Itzhak et al., 1985; Alonso et al., 2000).

The endogenous ligand(s) for sigma receptors have yet to be conclusively identified. However, a number of candidates have been proposed including some neuroactive steroids, sphingolipids (Su et al., 1988; Ramachandran et al., 2009), and most recently *N*,*N*-dimethyltryptamine (DMT) (Fontanilla et al., 2009). While neuroactive steroids undoubtedly play a significant role in brain physiology, the complexity of their interactions with multiple receptor systems and HPA function makes definitive assignment of their actions to specific processes a challenge. Nevertheless, cross pharmacology between neurosteroids and sigma ligands has been reported and antidepressant effects elicited by exogenously administered neurosteroids can be antagonized by sigma ligands. Studies of the role of neurosteroids in depression and as sigma receptor effectors are the subject of several reviews (van Broekhoven and Verkes, 2003; Maurice, 2004; Monnet and Maurice, 2006; Dhir and Kulkarni, 2008a). The roles of other putative endogenous sigma ligands are unknown at this time.

Two subtypes of sigma receptors, sigma-1 and sigma-2, have been identified, and are differentiated by their molecular weights, tissue distributions, and pharmacological profiles (Hellewell, 1990; Quirion et al., 1992; Hellewell et al., 1994; McCann et al., 1994). There is some evidence for additional subtypes of sigma receptors, but thus far they remain poorly characterized (Kovacs and Larson, 1995; Bergeron and Debonnel, 1997; Wolfe et al., 1997). Both currently identified subtypes appear to convey antidepressant properties, but research on sigma receptors has been biased toward the sigma-1 subtype primarily due to the availability of a significant number of ligands with high affinity and selectivity, and due to its successful cloning.

The sigma-1 receptor is a highly conserved 223 amino acid protein that has been cloned from several species, including rodents and humans (Hanner et al., 1996; Kekuda et al., 1996; Seth et al., 1997; Seth et al., 1998; Mei and Pasternak, 2001). Functionally, sigma-1 receptors appear to operate primarily via protein-protein interactions and have been shown to modulate the activity of various ion channels and signaling molecules (Maurice and Su, 2009). Sigma-1 receptors are expressed on the endoplasmic reticulum (ER) and can

translocate between different cellular compartments in response to ligand binding (Morin-Surun et al., 1999; Hayashi and Su, 2003; Mavlyutov and Ruoho, 2007). Accordingly, the discrete activities that are ascribed to the sigma-1 receptor depend on its cellular location. Sigma-1 mediated modulation of ion channels on the plasmalemma (Yamamoto et al., 1995; Lupardus et al., 2000; Aydar et al., 2002; Tchedre et al., 2008; Johannessen et al., 2009) and control of intracellular calcium via interactions with inositol trisphosphate (IP_3) receptors on the ER are well documented (Novakova et al., 1998; Hayashi et al., 2000; Hayashi and Su, 2001; Hayashi and Su, 2007; Wu and Bowen, 2008). Likewise, a recent report details a chaperone-like activity for sigma-1 receptors, whereby its association with IP_3 receptors at the mitochondrial associated membrane (MAM) facilitates efficient Ca^{2+} signaling from the ER to the mitochondria, suggesting that sigma receptors play an important role in bioenergetics (Hayashi and Su, 2007).

The sigma-2 receptor has not yet been cloned but is thought to be 18–22 kDa protein that is enriched in lipid rafts, where it affects Ca^{2+} signaling through sphingolipid products (Crawford et al., 2002). The role of sigma-2 receptors in depression is not as well defined as that of sigma-1, although one report suggests that the sigma-2 selective ligand siramesine (Lu 28–179; 19-[4[1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-butyl]spiro[isobenzofuran-1(3H), 49-piperidine]) shows equivalent antidepressant activity compared to the established antidepressants citalopram and imipramine in a chronic mild stress model in mice (Sanchez and Papp, 2000).

3. Involvement of sigma receptors in the actions of antidepressant drugs

3.1. Interaction of antidepressant drugs at sigma receptors

The involvement of sigma receptors in the actions of antidepressant drugs was first suggested by observations that most marketed antidepressant drugs bind to these receptors, raising the possibility that some of their therapeutic effects may be mediated via these proteins (Schmidt et al., 1989; Itzhak and Kassim, 1990; Narita et al., 1996). Table 1 summarizes representative tricyclic antidepressants, MAOIs, SSRIs and newer generations of antidepressant drugs that have significant affinity for sigma receptors, particularly the sigma-1 subtype. In addition to the classical antidepressants, neurosteroids with antidepressant activity such as dehydroepiandrosterone (DHEA) and pregnenolone, bind to sigma receptors (Su et al., 1988; Su et al., 1990; Maurice, 2004) and the putative active constituent of St. John's wort, an herbal treatment for depression (Mennini and Gobbi, 2004), has also been shown to possess significant affinity for sigma receptors (Raffa, 1998; Perfumi et al., 2001). More recently, direct evidence for the *in vivo* binding of the high affinity sigma ligand and SSRI, fluvoxamine, to sigma receptors, has been reported (Ishikawa et al., 2007). In this study, human volunteers were subjected to positron emission tomography with the high affinity sigma-1 selective radioligand [^{11}C]SA 4503 (1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride) prior to and following oral administration of fluvoxamine or paroxetine. The results conclusively show displacement of the radioimaging agent by fluvoxamine, but not by paroxetine, an SSRI which exhibits negligible affinity for the sigma-1 receptor (Ishikawa et al., 2007).

3.2. Effects of a sigma receptor agonist in depressed humans

The sigma receptor agonist, igmesine hydrochloride [JO 1784; (+)-*N*-cyclopropylmethyl-*N*-methyl-1,4-diphenyl-1-ethylbut-3-en-1-ylamine hydrochloride] exhibits high affinity for the sigma-1 receptor (IC_{50} of 39 ± 8 nM in rat brain membrane). In an early Phase II open-label study, 31 severely depressed in-patients showed significant improvement for up to four weeks when treated with igmesine (Pande et al., 1999; Volz and Stoll, 2004). Following this study, igmesine was tested in a 6-week, multi-center, double blind, placebo-controlled study in 348 patients meeting the DSM-IV criteria for major depression (Pande et al., 1999; Volz and Stoll, 2004). In this study, igmesine (25 or 100 mg/day) was as effective as fluoxetine (qd, 20 mg/day), as measured using the Hamilton Depression Rating Scale (HAM-D score) (Pande et al., 1999; Volz and Stoll, 2004). Adverse events were reported in 50% and 62% of igmesine patients (25 and 100 mg/day, respectively), as compared to 66% and 53% of fluoxetine- and placebo-treated patients (Pande et al., 1999; Volz and Stoll, 2004). These data indicate that a selective sigma receptor agonist produces antidepressant effects in humans, with comparable efficacy to a well established, marketed medication.

3.3. Specificity of sigma agonist actions in producing antidepressant-like effects

Because most clinically-used antidepressant drugs interact with a variety of protein targets, appropriate tests of selective sigma receptor agonists were needed to conclusively associate sigma proteins with antidepressant effects. Accordingly, to determine if the activation of sigma receptors alone was sufficient to produce antidepressant actions, a series of preclinical studies was performed using the established rodent models, the forced swim test (FST) and the tail suspension test (TST) (Porsolt et al., 1977; Steru et al., 1985). The FST and TST are not depression models per se, but do exhibit robust and reproducible responses to currently known antidepressant treatments following acute dosing (Porsolt et al., 1977; Steru et al., 1985). In these tests, antidepressant-like effects were observed for several selective sigma receptor agonists and putative agonists including: di-o-tolylguanidine (DTG), igmesine, (+)-pentazocine, SA 4503, and UMB23 (1-(3-phenylpropyl)piperidine oxalate) (Matsuno et al., 1996; Wang et al., 2007a). Pre-treatment with the sigma receptor antagonists BD1047 (N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino)ethylamine) or NE-100 (N,N-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine) abolished the antidepressant-like actions of the sigma receptor agonists, confirming the involvement of sigma receptors (Matsuno et al., 1996; Wang et al., 2007a). Studies with sigma-1 receptor knockout mice further support the role of these proteins in depression as these mice present a depression-like response in the FST (Sabino et al., 2009).

While the vast majority of clinically-used antidepressant drugs interact with sigma receptors, there are some exceptions. Paroxetine (SSRI) and desipramine (tricyclic antidepressant) have weak affinity for sigma receptors, yet are known to produce robust antidepressant effects in humans (Barringer, 1965; Caley and Weber, 1993; Narita et al., 1996). Therefore, activation of sigma receptors does not appear necessary for conveying therapeutic benefits. While not necessary, it is important to note that their activation alone appears sufficient for producing antidepressant-like effects.

Whereas many studies indicate that sigma receptor agonists evoke antidepressant actions, the specific mechanisms underlying these therapeutic effects have yet to be fully elucidated. Therefore, the remainder of this review summarizes data demonstrating that sigma receptor agonists promote processes and neural adaptations that elicit antidepressant effects.

4. Conceptual framework for the mechanism(s) of action of antidepressant drugs

No new, unique class of antidepressant drug has been introduced in the last 20 years (Berton and Nestler, 2006; Mathew et al., 2008). Yet, there have been significant advancements in our understanding of the basic neurobiology that underlies the actions of antidepressant medications (Manji, 2001; Nestler, 2006; Krishnan, 2008). The delayed onset of clinical effects (weeks to months) for drugs targeting monoaminergic systems suggest that antidepressant effects are not mediated solely by the acute alteration of neurotransmitter levels. Current theories take into consideration the complexity of changes in interneuronal transmission, intracellular signaling and neuronal structure that may accompany antidepressant treatment (Duman, 2004; Dranovsky and Hen, 2006; Warner-Schmidt and Duman, 2006; Dougherty and Rauch, 2007; Tanis and Duman, 2007; Tanis et al., 2007; McClung and Nestler, 2008). Consequently, the term “hypothesis of neuroplasticity” has been proposed to capture the diversity of these dynamic changes (Racagni and Popoli, 2008).

Figure 1 summarizes the hypothesized actions promoted by antidepressant medications, which are separated temporally into immediate, intermediate, and delayed effects. When antidepressant drugs bind to monoamine reuptake sites, sigma receptors, and other neurotransmitter receptors, immediate acute changes in neurotransmission are induced (Skuza, 2003; Berton and Nestler, 2006; Hayashi and Su, 2008; Mathew et al., 2008). The resulting activation of intracellular signaling cascades elicits a number of effects, including changes in Ca^{2+} levels, phosphorylation of effector proteins and transcription factors, and ultimately, modification of gene expression (Popoli, 2002; Tanis and Duman, 2007; Racagni and Popoli, 2008). These alterations may evoke persistent changes in the levels and activities of 1) neurotransmitters, 2) neurotransmitter receptors and transporters, 3) transcription factors such as cyclic adenosine monophosphate response element binding protein (CREB), and 4) growth factors, such as brain derived neurotrophic factor (BDNF) (McClung and Nestler, 2008; Racagni and Popoli, 2008). The resulting upregulation of gene function may also facilitate structural alterations that enhance synaptic plasticity, including increased synapse formation, spine density, neurite sprouting and elongation, and neurogenesis (Duman, 2001; Racagni and Popoli, 2008). The ability of antidepressant drugs to promote these structural/morphological changes in the brain may help to restore normal functions in depressed individuals where neuronal damage or dysregulated signaling has compromised function.

Sigma receptor agonists have the ability to promote key neural adaptations that are characteristic of antidepressant drugs. Moreover, sigma-mediated events may occur at multiple points in the cascade of effects elicited by antidepressant medications. The specific mechanistic details through which these effects are elicited may differ somewhat from those

currently attributed to existing antidepressant medications but the functional outcomes are hypothesized to be similar.

5. Mechanisms of antidepressant-like actions of sigma receptor agonists

5.1. Modulation of classical neurotransmitter systems

5.1.2. Glutamatergic modulation—Accumulating evidence indicates that NMDA receptor function, and glutamatergic signaling in general, are compromised in depression, and that modulation of glutamatergic neurotransmission contributes to the therapeutic effects of antidepressant drugs (Skolnick, 2002; Paul and Skolnick, 2003; Hashimoto, 2009; Machado-Vieira et al., 2009b; Skolnick et al., 2009). It is therefore significant that glutamatergic responses that are mediated through NMDA receptors can be modulated by sigma receptor ligands, where activation of sigma receptors results in enhanced NMDA neurotransmission (Iyengar et al., 1990; Monnet et al., 1990; Monnet et al., 1992b; Bergeron et al., 1993; Bergeron et al., 1995; Yamamoto et al., 1995; Debonnel and de Montigny, 1996; Gronier and Debonnel, 1999; Guitart et al., 2000; Bermack et al., 2002; Bermack and Debonnel, 2005; Martina et al., 2007). This enhanced NMDA neurotransmission may facilitate compensatory glutamatergic signaling in systems compromised by depressive pathology.

The potentiation of glutamatergic responses in hippocampal neurons *in vivo* via NMDA receptors following application of sigma-1 agonists is well established (Monnet et al., 1990; Monnet et al., 1992b; Bergeron et al., 1993; Bergeron et al., 1995). Recent investigations using whole cell patch techniques have identified specific currents that mediate these responses. In particular, small conductance Ca^{2+}-activated K^+ channels (SK channels) are implicated in the sigma-mediated potentiation of NMDA responses in CA1 pyramidal cells (Martina et al., 2007). Blockade of SK channels using the sigma receptor agonist (+)-pentazocine increases Ca^{2+} influx through NMDA receptors, resulting in enhanced NMDA-mediated responses and long-term potentiation (Martina et al., 2007). Control and antagonism studies further confirm that intracellular Ca^{2+} and Ca^{2+} influx through NMDA receptors is required for the (+)-pentazocine effect, which can be antagonized with haloperidol through non-dopaminergic, presumably sigma-mediated, mechanisms. Together with earlier studies demonstrating the ability of fluoxetine to block SK channels (Terstappen et al., 2003), and the importance of the hippocampus to depression pathophysiology (Duman et al., 1997; Nestler et al., 2002; Sheline et al., 2003; Stockmeier et al., 2004; Hercher et al., 2009), these data suggest a potential mechanism through which sigma receptors may promote therapeutically relevant effects.

Chronic administration of SA 4503, a putative sigma receptor agonist, elicits antidepressant-like effects in a variety of animal models; it also produces therapeutically relevant alterations in NMDA receptor expression in mice that have undergone an olfactory bulbectomy (OB) (Wang et al., 2007a). OB, a procedure that simulates many pathophysiological changes that characterize major depression in humans, also produces diminution of NMDA receptor expression in mice (Webster et al., 2000; Ho et al., 2001; Robichaud et al., 2001). Two weeks of chronic treatment with SA 4503 reverses the diminished expression of NMDA NR1 subunits in the prefrontal cortex, hippocampus, and

amygdala of OB mice (Wang et al., 2007a). No effects on NR2A or NR2B subunits are observed (Wang et al., 2007a). The enhancement by SA 4503 of NR1 expression in OB mice is prevented with the sigma receptor antagonist, NE-100 (Wang et al., 2007a). In contrast, desipramine, an antidepressant drug that has weak affinity for sigma receptors does not show NR1 enhancing activity (Wang et al., 2007a). Together, these studies suggest that the enhancement of NMDA-mediated responses by sigma receptor agonists may be a contributing mechanism for sigma receptor elicited antidepressant-like effects.

A number of other effectors of glutamate neurotransmission have demonstrated antidepressant activity. NMDA antagonists such as ketamine have been reported to produce antidepressant effects in animal models and humans (Kugaya, 2005; Zarate et al., 2006; Machado-Vieira et al., 2009a), presumably through downstream activation of AMPA receptors. This is consistent with the antidepressant-like activity of positive AMPA modulators in animal models (O'Neill and Witkin, 2007). Antidepressant-like effects have also been observed in rodents following antagonism of metabotropic glutamate receptors (Kugaya, 2005; Pilc et al., 2008; Hashimoto, 2009). This includes antagonism of the presynaptic Group II autoreceptors (mGluR2 and mGluR3), which results in increased glutamatergic neurotransmission (Chaki et al., 2004). Reports of the antidepressant activity of the NMDA glycine binding site partial agonist, D-cycloserine, in humans (Crane, 1959) and rodents (Papp and Moryl, 1996; Lopes et al., 1997) also suggests a role for modulation of NMDA activity in antidepressant effects.

The complexity of glutamatergic signaling supports the possibility of multiple mechanisms that promote antidepressant activity. This may explain the seemingly contradictory antidepressant activities of reduced NMDA function via antagonists vs. enhanced NMDA transmission via sigma receptor activation. Additional studies to further characterize interactions between sigma receptors and NMDA, and non-NMDA glutamatergic mechanisms, are warranted.

5.1.2. Serotonergic modulation—The therapeutic effects of chronic administration of antidepressant drugs are associated with an enhancement of serotonin neurotransmission (Blier and Bouchard, 1994; Blier and de Montigny, 1994; Owens, 1996). Acute administration of antidepressant drugs, such as SSRIs, causes a reduction in the firing of serotonergic neurons, which recover with long term administration (Chaput et al., 1986; Beique et al., 2000). This recovery in firing of serotonin neurons is thought to develop after desensitization of somatodendritic 5-HT_{1A} autoreceptors, activated in response to serotonin released from axon collaterals (Blier and de Montigny, 1994). This phenomenon has been proposed as a mechanism that explains the three to four week delay in clinical efficacy of antidepressant drugs (Chaput et al., 1986; Blier and de Montigny, 1994). In contrast to the delayed effects of SSRIs, the well established selective sigma receptor agonists DTG and (+)-pentazocine increase the firing of serotonergic neurons in the dorsal raphe nucleus (DRN) of anesthetized rats with only two days of treatment (Bermack and Debonnel, 2001). Further, this result was maintained following 21 days of sigma agonist treatment (Bermack and Debonnel, 2001). These rapid effects elicited by DTG and (+)-pentazocine appear to be mediated through sigma receptors because they can be prevented by co-administration of the sigma receptor antagonist, NE-100 (Bermack and Debonnel, 2001). The selective sigma

receptor agonist SA 4503 also produces significant increases in the firing rate of DRN neurons after two days of treatment (Lucas et al., 2008). This sigma receptor-induced enhancement in serotonergic neuronal function has been proposed to facilitate a more rapid onset of antidepressant efficacy as compared to existing medications, and may also contribute to added efficacy by targeting new mechanisms (Bermack and Debonnel, 2001).

A compelling series of experiments suggests that a synergistic antidepressant effect can be elicited following simultaneous agonism of 5-HT_{1A} and sigma receptors. Administration of a single oral dose of OPC-14523 ([1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-methoxy-3,4-dihydro-2-quinolinone monomethanesulfonate), a combined SSRI/5-HT_{1A} agonist/sigma-1 agonist, produces antidepressant-like effects in mice in the FST, whereas established antidepressant drugs such as fluoxetine or imipramine require four days to elicit a similar effect (Tottori et al., 2001). The behavioral effects of OPC-14523 are attenuated by either the sigma-1 receptor antagonist NE-100 or the selective 5-HT_{1A} antagonist WAY-100635 (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinylcyclohexanecarboxamide maleate), indicating that both receptor systems are important contributors to the observed effects (Tottori et al., 2001). More recent experiments confirm that the behavioral effects of OPC-14523 can be duplicated with the combined administration of sub-effective doses of the 5-HT_{1A} agonist 8-OH-DPAT (8-hydroxy-N,N-dipropyl-2-aminotetralin) and a sigma receptor agonist such as DTG or SA 4503 (Skuza and Rogoz, 2007). In electrophysiological studies, OPC-14523 increases serotonergic neurotransmission in the DRN, and this effect is blocked with the sigma receptor antagonist NE-100 (Bermack et al., 2004). Together, the data demonstrate sigma receptor-mediated modulation of serotonergic functions. The enhanced effects following stimulation of both $5HT_{1A}$ and sigma receptors suggest a potential novel pharmacotherapeutic strategy for future antidepressant development.

5.1.3. Catecholaminergic modulation—Current therapeutic strategies also exploit modulation of catecholaminergic systems to effect antidepressant activities. These strategies are supported by evidence for the involvement of dopamine and norepinephrine in the actions of SSRIs, MAOIs, and TCAs (Dailly et al., 2004; Nutt, 2006). Selective reuptake inhibitors for norepinephrine (NRIs) and combination reuptake inhibitors for serotonin/norepinephrine (SNRIs) and norepinephrine/dopamine (NDRIs) are also in clinical use. Therefore, it is noteworthy that the actions of two clinically relevant catecholaminergic-targeted antidepressant medications, bupropion and venlafaxine, can be modulated through sigma receptors (Dhir and Kulkarni, 2007; Dhir and Kulkarni, 2008b). Potential mechanisms through which sigma receptors modulate catecholaminergic neurotransmission have been studied in both *in vitro* and *in vivo* systems.

A number of *in vitro* studies have examined the role of sigma receptors on NMDA-stimulated release of catecholamines. The effects of sigma ligands on NMDA-stimulated release of [^{3}H]norepinephrine from rat hippocampal slices produced conflicting results, with sigma agonists potentiating release in the hands of one research group (Monnet et al., 1992a; Monnet et al., 1996) and inhibiting release in the hands of another group (Gonzalez-Alvear and Werling, 1995b). The disparate results are likely due to differences in the amount of NMDA utilized for stimulation but together provide evidence that sigma ligands are capable

of modulating norepinephrine release in the hippocampus with the caveat that the results observed are highly dependent on experimental conditions (Matsumoto et al., 2007). Similar studies have investigated sigma receptor-mediated modulation of NMDA-stimulated release of [^{3}H]dopamine from rat and guinea pig striatal slices (Gonzalez-Alvear and Werling, 1994; Gonzalez-Alvear and Werling, 1995a; Gonzalez and Werling, 1997; Nuwayhid and Werling, 2003). The consensus from these studies is that sigma receptor agonists inhibit NMDA-stimulated release of striatal dopamine and that this effect can be reversed by application of sigma receptor antagonists (Gonzalez-Alvear and Werling, 1994; Gonzalez-Alvear and Werling, 1995a; Gonzalez and Werling, 1997; Nuwayhid and Werling, 2003).

In vivo studies also support the involvement of sigma receptors in the modulation of dopamine release in the rat brain. Microdialysis studies reveal increases in extracellular dopamine in the striatum of awake, freely moving animals following intraperitoneal (i.p.) injection of the sigma receptor agonists (+)-pentazocine or DTG (Patrick et al., 1993). Similarly, following subcutaneous (s.c.) injection, (+)-pentazocine or (+)-SKF 10,047 increases dopamine in the striatum and medial prefrontal cortex, but (−)-SKF 10,047 or DTG produces no changes (Gudelsky, 1995). The release of striatal dopamine appears to be sigma-mediated because NE-100 can antagonize the changes resulting from acute oral administration of SA 4503 (Kobayashi et al., 1997). The more direct application of (+)-pentazocine or DTG by intrastriatal infusion in rats produces a biphasic effect, with an initial increase in extracellular dopamine in the striatum in the first 30 minutes, followed by a decrease in the subsequent 90 minutes following continuous infusion (Gudelsky, 1999). These studies provide evidence that sigma receptors can modulate catecholamine release in specific areas of the brain; however, the mechanisms involved and the impact on depression pathology remain unknown.

5.2. Modulation of signaling pathways

Intracellular second messenger signaling pathways are activated by classical neurotransmitters and neurotrophic factors via membrane associated receptors that can be modulated by sigma receptors. Activation of these signaling cascades affects a multitude of divergent but interrelated pathways which serve the common function of regulating downstream proteins such as transcription factors, which facilitate neuroplasticity and altered central nervous system functioning (Figure 2). The following sections summarize the major features of each of these systems and the potential role of sigma receptors.

5.2.1. Classical neurotransmitter signaling pathways—Classical neurotransmitters including glutamate, serotonin and norepinephrine, activate key signaling pathways implicated in the actions of antidepressant drugs, including the phosphoinositide second messenger system and the cyclic adenosine monophosphate (cAMP) pathway (Tanis and Duman, 2007). The initiation of these signaling cascades promotes the subsequent activation of protein kinases, including protein kinase C (PKC), protein kinase A (PKA), and calmodulin dependant protein kinase (CAMK) that phosphorylate downstream targets such as cytoskeletal proteins and transcription factors (Tanis and Duman, 2007). The activities of sigma receptor agonists appear to engage these same pathways by modulating intracellular Ca^{2+} or by affecting protein kinase activity.

The sigma-1 receptor modulates intracellular Ca^{2+} primarily through interactions with IP_3 receptors on the ER and through interactions with Ca^{2+} channels on the plasma membrane (Hayashi et al., 2000; Hayashi and Su, 2007; Martina et al., 2007). Activation of sigma-1 receptors causes the dissociation of ankyrin B from IP_3 receptors, resulting in disinhibition of IP_3 receptors and potentiation of Ca^{2+} signaling from the ER to the cytosol (Hayashi and Su, 2001). As mentioned previously, sigma receptor-induced potentiation of Ca^{2+} entry into the cell can occur via sigma receptor agonist-stimulated enhancement of NMDA function, through the blockade of SK channels (Martina et al., 2007).

In addition to affecting the function of IP_3 receptors, the sigma-1 receptor engages the phosphoinositide pathway through upregulation of phospholipase Cβ (PLCβ), and modulation of PKC activity (Romero et al., 2000; Monnet et al., 2003; Nuwayhid and Werling, 2003; Kim et al., 2008). The sigma receptor ligand E-5842, (4-[4-fluorophenyl]-1,2,3,6-tetrahydro-1-[4-{1,-2,4-triazol-1-1}butyl]pyridine citrate) can upregulate PLCβ in the frontal cortex with a concomitant increase in PLCβ activity (Romero et al., 2000). This increase in PLCβ activity correlates with an increase in phosphoinositide second messenger signaling. However, it has not been conclusively demonstrated that these effects are due to the activity of sigma receptors because no attempt has yet been made to antagonize this activity (Romero et al., 2000). Sigma-1 receptors are also involved in several processes mediated through PKC pathways. In rat hippocampal pyramidal neurons, the sigma-1 receptor agonist (+)-pentazocine potentiates glutamate elicited increases in intracellular Ca^{2+}, an effect which can be inhibited with the sigma-1 antagonist NE-100 and the PKC inhibitor Gö-6976 (12-(2-cyanoethyl)-6,7,12,13-tetrahydro-13-methyl-5-oxo-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole) (Monnet et al., 2003). Inhibition of PKC was also shown to inhibit (+)-pentazocine-induced potentiation of NMDA stimulated [^{3}H]dopamine release from rat striatal slices (Nuwayhid and Werling, 2003). Inhibition of phospholipase C in this same series of experiments also negated the effects of (+)-pentazocine while having no effect on NMDA stimulation in the absence of (+)-pentazocine (Nuwayhid and Werling, 2003).

The cellular consequences of sigma receptor-mediated modulation of signaling are extensive. Increases in intracellular Ca^{2+} can lead to increased neurotransmission, neurite outgrowth, and calmodulin signaling. Sigma receptor ligand-induced Ca^{2+} release from the ER may also impinge on signaling cascades activated by growth factor binding to Trk receptors. These include PKC, MAPK, SAPK/JNK, and Akt-mediated pathways (Nishimura et al., 2008). It has been demonstrated that sigma-1 receptor-mediated effects on these pathways enhance neurite outgrowth; however, the full extent of sigma receptor-mediated activation of these pathways and subsequent gene expression has yet to be determined (Nishimura et al., 2008).

One potential consequence of the activation of these Ca^{2+}-dependant pathways is the modulation of gene expression by transcription factors such as CREB protein. A number of antidepressant drugs have been shown to regulate CREB (Carlezon et al., 2005; Nair and Vaidya, 2006; Tardito et al., 2006; Gass and Riva, 2007), which has been implicated in the expression of numerous genes involved in neuroplasticity and cell survival, including growth factors, which are further discussed in the next section.

Only one study specifically linking sigma receptors to the modulation of CREB has been reported to date. PPBP (4-phenyl-1-(4-phenylbutyl)piperidine), a prototypic sigma-1 receptor agonist, increases CREB phosphorylation (Yang et al., 2009). In this study, inhibitors for MAPK, MEK, CaMKII (Ca^{2+}/calmodulin dependent kinase II) and PI3-K (phosphoinositide 3-kinase) were ineffective in blocking PPBP-potentiated CREB phosphorylation while the PKA inhibitor, H89 (*N*-[2-(*p*-bromocinnamylamino)ethyl]-5-isoquinoline sulfonamide), and the sigma antagonist, rimcazole (9-{3-[(3*R*,5*S*)-3,5-dimethylpiperazin-1-yl]propyl}-9*H*-carbazole) prevented PPBP-mediated CREB phosphorylation (Yang et al., 2009). These results suggest that activation of sigma-1 receptors by PPBP stimulates CREB phosphorylation via a PKA-dependent pathway. Together, the data demonstrates the ability of sigma receptor ligands to modulate a variety of signaling cascades that are activated by classical neurotransmitter systems.

5.2.2. Neurotrophin and growth factor signaling pathways—Neurotrophins are extracellular signaling molecules with important roles in the development, growth, and maintenance of the central nervous system, promoting precursor proliferation, neuronal differentiation, and neuronal survival (Thomas and Peterson, 2008). In the brain, neurotrophins act through Trk receptors, with signaling achieved through PLC, Akt and MAP kinase pathways (Tanis and Duman, 2007; Tanis et al., 2007). Brain derived neurotrophic factor (BDNF) is the most widely studied neurotrophin in the context of depression research. In general, decreased levels of BDNF are associated with the pathophysiology of depression, while its upregulation is characteristic of antidepressant treatments (Racagni and Popoli, 2008).

A number of studies have demonstrated increased BDNF expression *in vivo* following chronic treatment with a variety of antidepressant drugs including MAOIs, SSRIs, and SNRIs (Duman and Monteggia, 2006). *In vivo* studies show that activation of TrkB, the primary receptor for BDNF, as well as TrkB-mediated PLCγ/IP_3/Ca^{2+} signaling, are common mechanisms of antidepressant drugs (Rantamaki et al., 2007). Additional evidence supporting a role for BDNF in antidepressant activity is provided by the observation that antidepressant drugs are ineffective in the FST in BDNF knockout mice and in TrkB-T1 transgenic mice which overexpress a truncated TrkB receptor (Martinowich et al., 2007). Overall, BDNF signaling and activation of the TrkB receptor are thought to be required for the behavioral effects of antidepressant drugs in rodents (Saarelainen et al., 2003; Castren and Rantamaki, 2008).

Sigma receptors have been implicated in both the upregulation of BDNF expression and in the potentiation of BDNF-activated PLCγ/IP_3/Ca^{2+} signaling pathways. Sigma-active antidepressant drugs such as imipramine and fluvoxamine potentiate BDNF-stimulated PLCγ activation in cultured cortical neurons, culminating in increased intracellular Ca^{2+} and glutamate release following chronic administration (Yagasaki et al., 2006). Evidence for the participation of sigma-1 receptors in these effects include: antagonism of imipramine-induced potentiation with the sigma-1 receptor antagonist BD1047, and enhancement of potentiation in cell cultures overexpressing sigma-1 receptors (Yagasaki et al., 2006).

Studies with the sigma-1 specific agonist, SA 4503, show that chronic, but not acute, dosing in adult rats increases the expression of BDNF in the hippocampus in a dose-dependent manner (Kikuchi-Utsumi and Nakaki, 2008). However, no increase of BDNF is observed in the striatum, midbrain, frontal cortex or thalamus in this study, suggesting that the BDNF changes are not a global effect of SA 4503 (Kikuchi-Utsumi and Nakaki, 2008).

In contrast to the effects of established antidepressant drugs, where increases in BDNF expression occur concomitantly with significant increases in hippocampal trkB mRNA and TrkB receptor expression (Nibuya et al., 1995), there appears to be a dissociation between the two endpoints for sigma receptor-mediated effects, where increases in hippocampal BDNF can be observed with no changes in TrkB receptor levels (Kikuchi-Utsumi and Nakaki, 2008). The impact and source of this difference in activities is unknown; however, the possibility that BDNF levels increase in response to sigma agonist-induced increases in glutamatergic neurotransmission has been proposed (Kikuchi-Utsumi and Nakaki, 2008).

An additional mechanism involving sigma receptors that potentially impacts levels of BDNF may be produced through activator protein 1 (AP-1). AP-1 is a transcription factor important in cellular differentiation, proliferation, and in the regulation of sigma-1 receptor expression (Seth et al., 1997; Prasad et al., 1998; Shaulian and Karin, 2001). Studies in a rat primary cerebellar neuron culture demonstrate that both AP-1 and cAMP-responsive element (CRE) dependent transcription can be stimulated by BDNF through cAMP independent pathways (Gaiddon et al., 1996). Furthermore, increased binding of AP-1 in the hippocampus has been observed following direct infusion of BDNF in rat dentate gyrus (Okamoto et al., 2003). Hence, upregulation of BDNF via antidepressant or sigma agonist treatment may contribute to increased levels of sigma-1 receptors, and CRE-related gene products, including BDNF, in a feed forward loop that does not require cAMP signaling.

5.4. Modulation of structural changes

The ability of antidepressant drugs to activate CREB and stimulate neurotrophic factor production and signaling may facilitate alterations in neuronal cell morphology and proliferation, which are described in detail in the next two sections.

5.4.1. Neurite sprouting—PC12 cells are a clonal rat adrenal pheochromocytoma line that differentiate in response to nerve growth factor (NGF), producing processes analogous to those formed by sympathetic neurons in primary cell culture. Thus, NGF-stimulated PC12 cultures serve as an accepted model for neuronal differentiation (Greene, 1976). The sigma-active antidepressant drugs fluvoxamine and imipramine enhance NGF-induced neurite sprouting in PC12 cells (Takebayashi et al., 2002). Similar effects are produced with the selective sigma-1 receptor agonist (+)-pentazocine, suggesting that activation of sigma receptors alone, particularly the sigma-1 subtype, can stimulate structural modifications that may impart antidepressant efficacy (Takebayashi et al., 2002). Similar neuroadaptations observed in cultured cortical rat neurons appear to involve modulation of BDNF signaling and glutamate release (Takebayashi et al., 2002; Yagasaki et al., 2006). Antagonists such as BD1047 and NE-100 attenuate these effects, as does an antisense oligonucleotide targeted to sigma-1, further implicating sigma receptors in these processes (Takebayashi et al., 2002;

Yagasaki et al., 2006). Additional evidence for the involvement of sigma-1 receptors in the potentiation of NGF-induced neuronal growth includes: 1) upregulation of sigma-1 receptors following chronic antidepressant or (+)-pentazocine treatment, 2) enhanced neurite sprouting in cells overexpressing sigma-1, and 3) reduced NGF-induced neurite growth in sigma-1 antisense treated cells (Takebayashi et al., 2002).

More recent studies demonstrate similar potentiation of NGF-stimulated neurite growth for the sigma-1 specific ligand SA 4503, and implicate some of the specific signaling pathways involved. Antagonism of the actions of SA 4503 is effected with the sigma receptor antagonist NE-100, the IP_3 receptor inhibitor xestospongin, as well as by specific inhibitors of signaling pathways downstream from the NGF receptor, TrkA (Nishimura et al., 2008). Reversal of the sigma-1-mediated effects with xestospongin is consistent with the involvement of a sigma receptor/IP_3 interaction in the observed potentiation of NGF-induced neurite growth. Similarly, antagonism of the SA 4503-elicited effect by inhibition of proteins involved in downstream signaling from the TrkA receptor supports the inference that sigma receptor activation results in a positive modulatory effect on the TrkA pathway (Nishimura et al., 2008).

The sigma receptor has also been implicated in the potentiation of NGF-induced neurite outgrowth that is elicited by donepezil, an acetylcholinesterase inhibitor marketed for the treatment of Alzheimer's associated dementia (Oda et al., 2007; Ishima et al., 2008). Donepezil has demonstrated efficacy in the FST in mice (Maurice et al., 2006) and displays high binding affinity (K_i = 14.6 nM) for the sigma-1 receptor, suggesting that its antidepressant effects are mediated, at least in part, by sigma receptors (Kato et al., 1999). As for SA 4503, antagonism of potentiation was achieved with either NE-100 or xestospongin (Ishima et al., 2008). Also consistent with the results observed with SA 4503, potentiation was associated with a concomitant increase in extracellular signal-regulated kinase (ERK) phosphorylation (Ishima et al., 2008), suggesting the involvement of the TrkA pathway. Thus, through activation of neurotrophin signaling pathways, sigma receptor ligands can promote neurite sprouting, a process which may aid in restoring synaptic function and cell morphology which has been compromised in depression.

5.5.2. Neurogenesis—Chronic treatment with antidepressant drugs upregulates expression of neurotrophic factors that support the growth of new neurons in the adult CNS (Duman and Monteggia, 2006; Martinowich et al., 2007; Balu et al., 2008). Neurogenesis is a complex multi-step process involving progenitor cell proliferation, differentiation, migration, neuronal maturation, and cell death (Balu, 2009). Hippocampal neurogenesis has been demonstrated following chronic antidepressant drug administration in rodents (Malberg et al., 2000) and tree shrews (Czeh et al., 2001), and following electroconvulsive shock in nonhuman primates (Perera et al., 2007). More recently, SSRI- and TCA-induced increases in neural progenitor cells in the dentate gyrus of humans was reported (Boldrini et al., 2009). Blocking neurogenesis can prevent the positive behavioral effects of antidepressants in animal models (Santarelli et al., 2003), suggesting that it can be an important component in the mechanism of antidepressant treatment (Perera et al., 2007; Sahay and Hen, 2007).

Continuous infusion of BDNF in the hippocampus of adult rats for two weeks results in the proliferation of newly formed hippocampal neurons (Scharfman et al., 2005). Therefore, the ability of antidepressant drugs to elicit neurogenesis may stem, at least in part, from their activation of neurotrophic factors. Because the sigma receptor agonist SA 4503 has been shown to upregulate BDNF in the hippocampus (Kikuchi-Utsumi and Nakaki, 2008), this may provide a mechanism through which sigma receptor agonists can promote neurogenesis.

As evidenced by increases in BrdU-labeled cells, cell proliferation has been observed in the hippocampus of rats treated chronically with representative antidepressant drugs such as tranylcypromine, reboxetine, fluoxetine, and fluvoxamine (Malberg et al., 2000; Manev, 2001). Similar studies have been performed with continuous administration of the sigma specific agonist SA 4503, eliciting significant increases in BrdU-staining cells in the subgranular zone (SGZ) of the hippocampus after three days of treatment (Lucas et al., 2008). Preliminary studies also confirm that administration of (+)-pentazocine, another sigma-1 receptor agonist, for 14 days, significantly augments the number of BrdU-positive cells in the hippocampus (Matsumoto and Yu, 2005).

Results of these studies provide evidence for the involvement of sigma receptors in neurogenesis. When considered as a whole, the data support an association between BDNF, neurogenesis, and the involvement of sigma receptors in the production of antidepressant-like actions.

6. Summary and conclusions

Antidepressant drugs stimulate a number of adaptive changes in the central nervous system. Among these changes are alterations in the function of neurotransmitter systems, particularly serotonin, norepinephrine, and glutamate. Antidepressant drugs also affect cellular plasticity by exerting actions through signaling molecules, transcription and neurotrophic factors. The importance of the ability of antidepressant drugs to promote structural changes, such as neuronal spouting and neurogenesis, in the CNS, has gained attention. With the growing acceptance that adaptive changes in the CNS are key contributors to the therapeutic actions of antidepressant drugs, the identification of new classes of compounds, such as sigma receptor agonists, that evoke such changes is of considerable interest, as they may represent novel antidepressant therapies.

Abbreviations

Akt	protein kinase β
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid
AP-1	activator protein 1
BD1047	N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino)ethylamine
BDNF	brain derived neurotrophic factor
CaMK	calmodulin dependant protein kinase

CaMKII	calmodulin kinase II
cAMP	cyclic adenosine monophosphate
CRE	cAMP-responsive element
CREB	cAMP response element binding
DHEA	dehydroepiandrosterone
DMT	*N*,*N*-dimethyltryptamine
DRN	dorsal raphe nucleus
DTG	di-o-tolylguanidine
EGF	epidermal growth factor
ER	endoplasmic reticulum
FST	forced swim test
GSK-3	glycogen synthase kinase 3
H89	*N*-[2-(*p*-bromocinnamylamino)ethyl]-5-isoquinoline sulfonamide
HAM-D	Hamilton Depression Rating Scale
HPA	hypothalamic-pituitary axis
IP_3	inositol 1,4,5-trisphosphate
MAM	mitochondrial associated membrane
MAOI	monoamine oxidase inhibitor
MAPK	mitogen activated protein kinase
MEK	mitogen/extracellular signal regulated kinase
NE-100	N,N-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine
NGF	nerve growth factor
NMDA	N-methyl-D-aspartate
NRI	norepinephrine reuptake inhibitor
OB	olfactory bulbectomy
PI3-K	phosphoinositol 3-kinase
PKA	protein kinase A
PKC	protein kinase C
PLC	phospholipase C
PPBP	4-phenyl-1-(4-phenylbutyl) piperidine
SA 4503	1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride
SNRI	serotonin-norepinephrine reuptake inhibitor

SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TST	tail suspension test
UMB23	1-(3-phenylpropyl)piperidine oxalate

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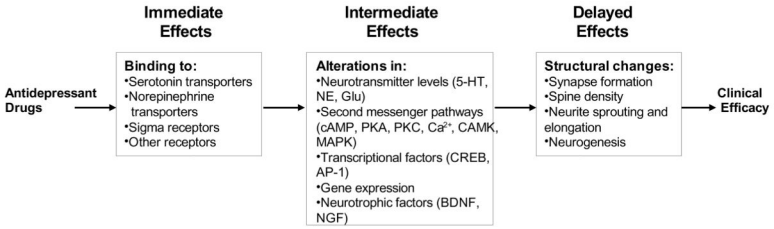

Figure 1. Hypothesized sequence of events for antidepressant actions

Classic antidepressant drugs produce effects which can be classified temporally into immediate, intermediate and delayed actions, with resulting functional changes associated at each stage.

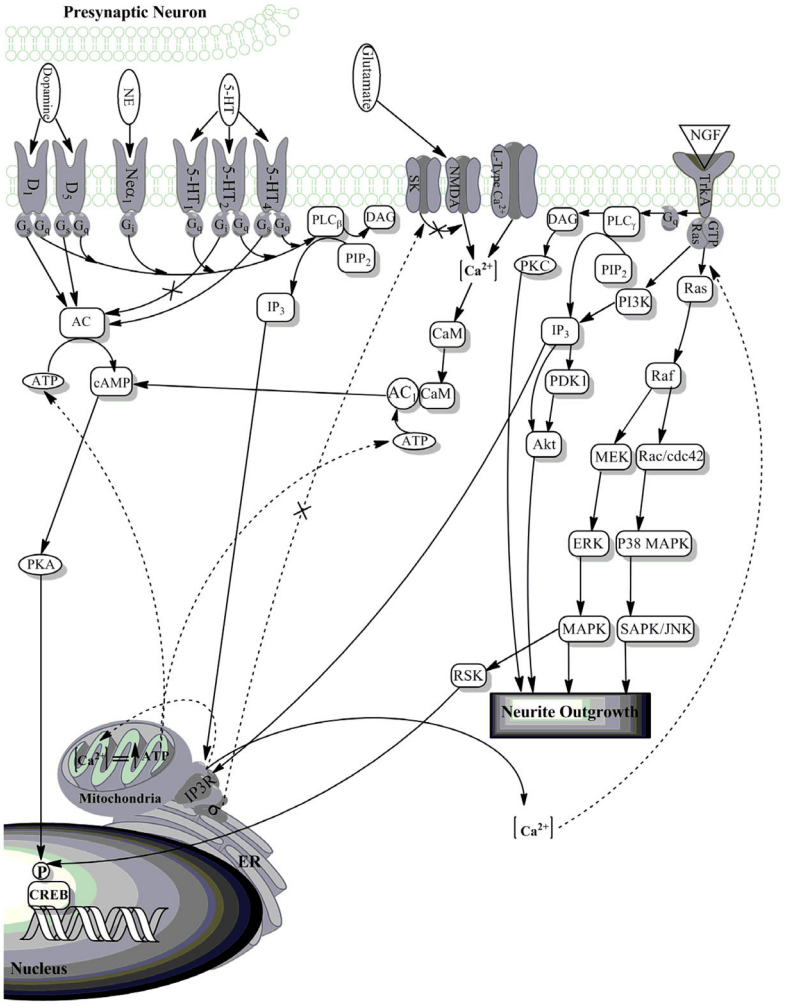

Figure 2. Sigma receptors modulate numerous pathways implicated in the etiology or pathophysiology of depression

It is believed that Ca2+ modulation through sigma receptors can act upon pathways involved in neurite outgrowth, as well as gene regulation, specifically, ERK, MAPK and Akt pathways. It is hypothesized that sigma receptor-mediated modulation of IP3Rs at the MAM, also contributes to an increase in ATP production from the mitochondria, which may have profound effects on signaling within the cell which have not yet been fully studied. Sigma receptors have also been shown to modulate PKA pathways; sigma agonists have been shown to modulate the phosphorylation of CREB, indicative of effects on gene transcription. Sigma receptors also have known effects on the transmission of signaling via neurotransmitters; however these pathways have not been fully elucidated. Dashed lines indicate known and hypothesized effects of sigma receptors on signaling pathways believed to be involved in depression.

Table 1

Representative compounds with affinity for sigma receptors.

Compounds	K_i (nM)		
	σ	$σ_1$	$σ_2$
SSRIs			
Fluvoxamine[1]		36	8,439
Sertraline[1]		57	5,297
S(+)-Fluoxetine[1]		120	5,480
Citalopram[1]		292	5,410
Paroxetine[1]		1,893	22,870
TCAs			
Opipramol[2]	50		
Imipramine[1]		343	2,107
Desipramine[1]		1,987	11,430
MAOIs			
Clorgyline[3]		2.9	505
(+)Deprenyl[3]		82	1,880
Harmaline[3]		310	2,100
Ro11-1163[3]		860	>50,000
Acetylcholinesterase inhibitor			
Donepezil[4]a	14.6		
Steroids			
Progesterone[5]		24.6	15,700
Deoxycorticorsterone[6]	938		
Dehydroepiandrosterone(DHEA)[7]	3,700		
Sigma compounds			
Haloperidol[8]		0.90	7.93
BD 1047[9]		0.93	9.15
NE-100[10]a		1.5	84.6
(+)Pentazocine[8]		1.62	728.4
SA4503[8]		4.63	63.09
(+)SKF 10,047[11]a		29	33,654
DTG[8]		35.45	39.87
Igmesine (JO1784)[12]a	39		
UMB23[13]		41	32
OPC-14523[14]a		47	56
St. John's Wort			

Compounds	K_i (nM)		
	σ	σ_1	σ_2
Hyperforin[15]a	1,400		
Hypericine[15]a	3,700		

Note:

a denotes IC_{50} in nM. σ denotes affinity for sigma receptors where affinity at individual subtypes has not been reported.

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