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Critical Review

The Role of Sigma Receptors in Depression

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Abstract. Behavioral models used to test potential antidepressants have shown that ligands that bind to sigma receptors possess "antidepressant-like" properties. The focus of this review is to discuss the literature concerning sigma receptors and their ligands, with respect to their antidepressants properties. In addition to the behavioral data, we discuss electrophysiological and biochemical models demonstrating sigma receptors' ability to modulate important factors in the pathophysiology of depression and/or the mechanisms of action of antidepressants such as the serotonergic neurotransmission in the dorsal raphe nucleus (DRN) and the glutamatergic transmission in the hippocampus. We also discuss the significance of these two systems in the mechanism of action of antidepressants. Sigma ligands have potential as antidepressant medications with a fast onset of action as they produce a rapid modulation of the serotonergic system in the DRN and the glutamatergic transmission in the hippocampus. As these effects of sigma ligands may produce antidepressant properties by completely novel mechanisms of action, they may provide an alternative to the antidepressants currently available and may prove to be beneficial for treatment-resistant depressed patients.

Keywords: sigma receptor, major depression, antidepressant, serotonin, glutamate, calcium regulation

1. Introduction and background

Since their discovery in 1976 (1), sigma receptors have remained an intriguing entity. As receptors they present very original aspects but are subjects of controversy regarding their identity(ies), their endogenous ligand(s), their role(s), and so on. Nearly thirty years after their initial description, a consensus has not yet been obtained, but some aspects have started to be more clearly established.

Sigma receptors were first classified as a subtype of opioid receptors (1). Later, the availability of newer and

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more selective ligands established sigma receptors as distinct from opiate receptors or the phencyclidine (PCP) binding site (2). Based on the pharmacological characteristics of several sigma ligands [sometimes not very selective such as the classical antipsychotic haloperidol (3)], sigma receptors were then further divided into two subtypes, denoted $sigma_1$ and $sigma_2$ (2). However, this classification remains unsatisfactory and there is debate over the existence of a third subtype ($sigma_3$) or an heterogeneity within the $sigma_1$ subtype. For example, radioligand binding studies with the prototypal sigma ligand [^{3}H](+)-pentazocine (4) have demonstrated that its binding sites are heterogenous. Specifically, (+)-pentazocine labeled a high and a low affinity site in several cell lines and the lower affinity site did not correspond to $sigma_2$ receptors (5, 6). In addition, a 3rd, intermediate site ($K_d = 30 – 60$ nM) was observed in human cell lines, suggesting a possible 3rd type of (+)-pentazocine binding site (5).

In keeping with the binding data, various electrophysiological data in the model of the modulation of the *N*-methyl-D-aspartate (NMDA) response of dorsal hippocampal pyramidal neurons from our laboratory suggest that the $sigma_1$ receptor does not represent a single entity. They indicate that (+)-pentazocine acts on a subtype of the sigma receptor different from that of other $sigma_1$ ligands such as JO-1784 (igmesine) (7), L-687,384 (8), and BD-737 (9). Moreover, Tsao and Su (10) purified a naloxone-sensitive, haloperidol-sensitive (+)-SKF-10,047 binding protein, which actually resembles the sigma opioid site originally proposed by Martin et al. (1), with high affinity for (+)-pentazocine but not for the other sigma ligands DTG (11), (+)-3-PPP (12), and progesterone (13).

1.1. Anatomical distribution of sigma receptors in the central nervous system (CNS)

Initial binding investigations, using the nonselective sigma ligand (+)-3-PPP, found the highest densities of binding in the spinal cord, pons-medulla, cerebellum, central gray, red nucleus, and hippocampus with moderate densities detected in the hypothalamus and cerebral cortex and low densities in the basal ganglia and thalamus (14).

Studies comparing $sigma_1$- versus $sigma_2$-receptor distributions found that $sigma_1$ sites were most abundant in the dentate gyrus of the hippocampus, facial nucleus, thalamic, and hypothalamic nuclei, with moderate densities found in the striatum, cerebellum, dorsal raphe nucleus (DRN), and locus coeruleus (15 – 17). In agreement, studies of $sigma_1$-receptor mRNA (messenger ribonucleic acid) levels found high levels of expression in all layers of the cerebral cortex, striatum, hippocampus, and cerebellum (18). $Sigma_2$ sites were found to be enriched in the substantia nigra, central gray matter, oculomotor nuclei, cerebellum, nucleus accumbens, amygdala, olfactory bulb, hippocampus, and motor cortex (15, 16, 19).

1.2. Potential endogenous ligands for sigma receptors

Early studies found that neurosteroids bind to $sigma_1$ receptors (20 – 22). For example, the neurosteroids progesterone and dihydroepiandrosterone sulfate (DHEAS) dose-dependently inhibit the in vivo binding of [^{3}H]-SKF-10,047, progesterone being the most potent (20 – 22).

These binding data led to the hypothesis that progesterone might be the endogenous ligand for $sigma_1$ receptors. This remains however controversial as the affinity of progesterone for sigma receptors does not appear very high for an endogenous ligand. Indeed, Schwarz et al. (23) argued that the concentration of endogenous progesterone, specifically the free serum concentration, was insufficient to occupy the sigma receptors in the brain, even during later pregnancy, when progesterone levels are at their highest. However, there are data suggesting that progesterone binds to sigma receptors under physiological conditions. It has been demonstrated that alterations in endogenous hormonal levels [e.g., adrenalectomy, castration, or ovariectomy (ADX, CX, or OVX, respectively), pregnancy, etc.] affect sigma ligands activity in several models such as the electrophysiological model of the modulation of the NMDA response in the hippocampus (24, 25) and the "antidepressant-like" effects of sigma ligands in behavioral models of depression (26). Moreover, radioligand binding studies show a 30 – 40% decrease in [^{3}H]SKF-10,047 binding during pregnancy, while ADX/CX enhanced [^{3}H]SKF-10,047 binding, whereas a subsequent treatment with finasteride, which increases progesterone levels, produced decreased [^{3}H]SKF-10,047 binding (22, 27).

At this point, the literature certainly supports the hypothesis that the endogenous ligand of sigma receptors could be a neurosteroid; however, it remains to be determined if it is really progesterone or perhaps one of its metabolites.

1.3. Pharmacology of sigma receptors

An interesting feature of sigma receptors is that in contrast with the classical pharmacology of many compounds that show a more less linear dose-response curve followed by a plateau effect, a biphasic bell-shaped dose response curve has been observed for sigma ligands in various behavioral, biochemical, and electrophysiological paradigms (28 – 31). For example, because of the

bell-shaped dose-response curves, in the electrophysiological paradigm of the modulation of the NMDA response (see below), low doses of sigma agonists induce a potentiation of the NMDA response (32, 33). At higher doses, the effects of sigma agonists such as DTG and JO-1784 progressively decrease and disappear (Fig. 1) and these molecules act as antagonists by preventing the potentiation induced by low doses of other sigma agonists (29). A similar bell-shaped dose-response curve has also been described with sigma ligands in other models such as in release experiments (30) and in behavioral models (28, 34). The exact reason for such bell-shaped dose-response curves obtained in so many models have not been well established. It has been proposed that they may be due to the fact that low doses of sigma ligands activate one subtype of sigma receptors for which they have high affinity, whereas higher doses may activate another/other subtype(s) of the sigma receptor for which they have a lower affinity, which would counteract the effects observed at lower doses (29, 35, 36). Nonetheless, it is important to note that the different (and sometimes opposite) results obtained with low and high doses of sigma ligands could constitute a very important factor to explain much of the controversy seen in the literature on sigma receptors.

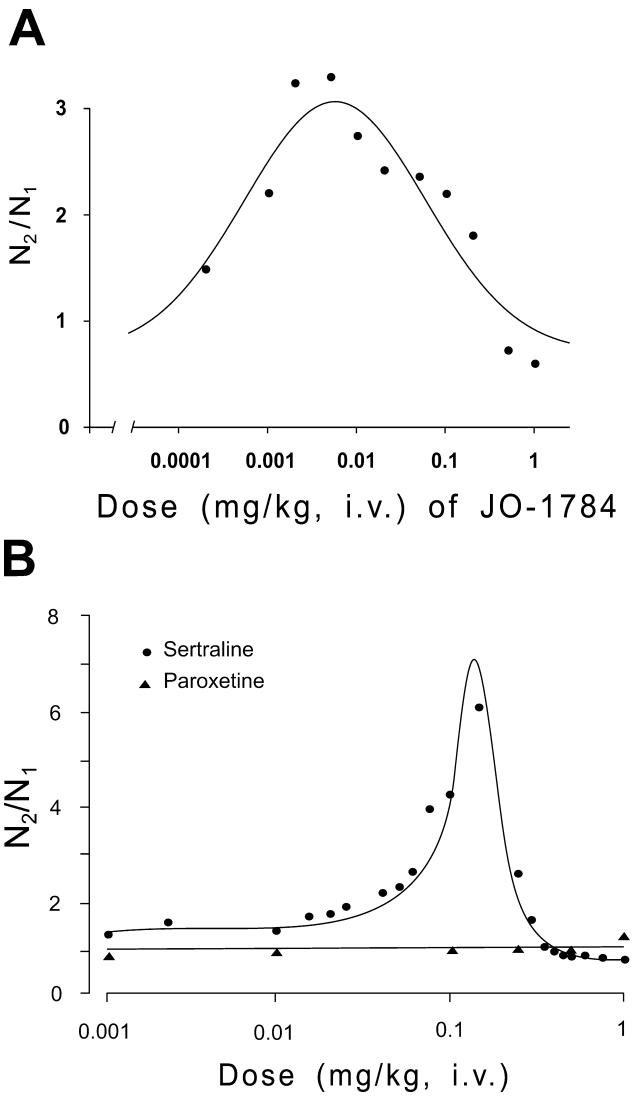

Fig. 1. Dose-response curve of the effects of intravenously administered igmesine (A) and of sertraline and paroxetine (B) on the neuronal activation of CA_3 dorsal hippocampus pyramidal neurons induced by microiontophoretic applications of NMDA. The effects of these drugs were assessed by determining the ratio (N_2/N_1) of the number of spikes generated/nC of NMDA before (N_1) and after (N_2) the injection of the drug. One dot represents the effect of one dose of drug administered to one rat while recording from one neuron. Adapted from refs. 29 and 35.

1.4. Cloning of the sigma$_1$ receptor

A significant breakthrough in sigma receptor research was the cloning of the sigma$_1$ receptor. It was cloned from guinea pig and mouse liver, human placental cell line and brain, and mouse and rat brain (37 – 41). The protein cloned was a 223 amino acid, 1 transmembrane protein with potent (+)-pentazocine, haloperidol, DTG, and (+)-3-PPP binding, but which did not couple with G-proteins (41, 42). The amino acid sequence of the sigma receptor cloned from the rat brain was highly homologous to the sigma receptor cloned from guinea pig liver and human placental cell line, but was not related to other known neurotransmitter receptors (37).

At this point, it is not completely clear whether the cloned sigma$_1$ receptor is the ligand binding subunit of a multi-subunit complex or represents one subtype of the sigma$_1$ receptor. Regardless, the cloning has led to an important focus on the molecular biology and signal transduction mechanisms of sigma$_1$ receptors. However, given the one-transmembrane segment cloned, it is most likely that it does not represent the complete functional receptor, but more experiments using techniques such as the use of selective sigma$_1$ receptor gene antisense will elucidate the exact structure of the functional sigma receptor in the future. A recent study investigating putative transmembrane segments based on homology identified two putative transmembrane segments for the sigma$_1$ receptor (43). Therefore, the exact structure of the sigma$_1$ receptor has yet to be fully elucidated.

The cloning of the sigma$_1$ receptor led to the development of sigma$_1$-receptor knockout mice (44). Preliminary studies of these mice determined that they display no significant phenotypic and no behavioral abnormalities under baseline conditions; however, further studies in various paradigms will be required to produce more insight into the functional roles of sigma$_1$ receptors.

2. Signal transduction by sigma receptors: interaction with G-proteins

The cloning of a one transmembrane domain sigma receptor, which could not correspond to a G-protein coupled receptor, reactivated the long-standing debate over whether or not sigma receptors act through G-protein-dependant signaling cascades. In support of sigma receptors' association with G-proteins, manipulating GTP and 5 guanylylimidodiphosphate [Gpp(NH)p] altered the binding of sigma ligands (45 – 47). Furthermore, there was a decreased responsiveness to guanine nucleotides following chronic treatments (48). Moreover, some selective sigma agonists were found to stimulate GTPase activity (49). Manipulation of G-proteins also altered sigma-mediated effects on potassium (K^+) currents (50), and NMDA-evoked release of [^{3}H]norepine phrine (NE) (51) and suppressed the neuronal response to NMDA (52), but had no effects on K^+ currents in other models or on the NMDA response with other sigma ligands (52 – 54). Contrasting results were also found for the effects of G-proteins on sigma ligand binding (55 – 57).

In conclusion, given the presumed heterogeneity of the $sigma_1$-receptor subgroup, it is likely that one subtype of the $sigma_1$ receptor interacts with G-proteins, while another subtype relies on G-protein-independent signal transduction mechanisms.

2.1. Modulation of K^+ currents

An interaction between sigma receptors and K^+ channels was suggested by the observation that the sigma ligands DTG and (+)-pentazocine inhibited K^+ currents (50, 53, 54). Further investigations of this modulation suggested that a protein-protein interaction is the likely mechanism of signal transduction by sigma receptors as sigma ligands did not interact directly with K^+ channels (43, 54). Furthermore, surprisingly sigma receptors were able to alter channel function in the absence of sigma ligands, suggesting that they are directly associated with K^+ channels, in a manner that can affect current flow, an effect which is enhanced in the presence of sigma ligands. Therefore, it has been suggested that sigma receptors may serve as auxiliary subunits to voltage-gated K^+ channels in the plasma membrane (43), which may involve other proteins such as ankyrin and inositol-1,4,5-trisphosphate (IP_3) receptors as suggested by Hayashi and Su (58).

2.2. Modulation of Ca^{2+} currents

An interaction between sigma receptors and Ca^{2+} channels was suggested by the observation that (+)-pentazocine inhibited the rise in Ca^{2+} levels induced by depolarization and that sigma ligands decreased basal intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), suggesting that sigma receptor activation alone affects $[Ca^{2+}]_i$ (59, 60). Sigma-induced increases in Ca^{2+} currents develop progressively following relatively long lasting applications of sigma ligands, suggesting a direct intracellular coupling of sigma receptors to Ca^{2+} channels, through which sigma ligands can stimulate voltage-activated Ca^{2+} conductances independent of the K^+ channel pathway (61).

Recently, several lines of evidence added further arguments for the involvement of $sigma_1$ receptors in Ca^{2+} signaling. Specifically, the $sigma_1$ ligands (+)-pentazocine and PRE-084 modulate Ca^{2+} signaling in NG108 cells via $sigma_1$ receptors by 2 different modes of action. Firstly, intracellularly, perhaps on the endoplasmic reticulum (ER), sigma ligands potentiate the bradykinin-induced increase in cytosolic free Ca^{2+} in a bell-shaped manner, which was blocked by $sigma_1$-receptor antisense (31). A second mode of action at the plasma membrane was demonstrated as (+)-pentazocine inhibits (in agreement with the effects observed in forebrain synaptosomes) (59, 60), while PRE-084 potentiates the depolarization-induced changes in Ca^{2+}, effects blocked by $sigma_1$-receptor antisense (31).

It has been proposed that the modulation of Ca^{2+} signaling described thus far involves the formation of a multi-protein complex. Specifically, $sigma_1$ receptors have recently been found to anchor ankyrin (a cytoskeletal adaptor protein) to the ER membrane and modulate the function of ankyrin and IP_3 receptor-3 on the ER (58). In this model, the presence of the sigma agonist (+)-pentazocine leads to the $sigma_1$ receptor /ankyrin complex dissociating from the IP_3 receptor-3. This dissociation leads to an increased binding of IP_3, which in turn increases Ca^{2+} efflux. On the other hand, in the presence of the $sigma_1$ antagonist NE-100 (62), the $sigma_1$ receptor dissociates from ankyrin, which remains coupled to IP_3 receptor-3 on the ER (58). This modulation of Ca^{2+} currents has important implications towards various cell functions including neurotransmitter release.

The data on the modulation of Ca^{2+} signaling by sigma receptors, similar to those with K^+ currents, suggests that $sigma_1$ receptors form multiunit complexes responsible for the modulation of ion channels. This formation of complexes with other proteins enables sigma ligands to exert a wide variety of actions in the CNS, so depending on the different combination of proteins formed, it is likely that different effector systems are activated, which then lead to different results. This hypothesis could also explain some of the discrepancies with respect to different signaling pathways observed to be

involved with the effects of $sigma_1$ ligands.

3. Glutamate and depression

Glutamate is the most widespread excitatory neurotransmitter in the CNS. Glutamate receptors have been pharmacologically classified as ionotropic and metabotropic receptors [reviewed by Bleich et al. (63)]. Ionotropic glutamate receptors include NMDA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate families of receptors. For the purpose of this review, we will focus on NMDA and AMPA receptors, as they have been linked to depression and/or antidepressant action (see below). NMDA receptors control channels that allow Na^+ and Ca^{2+} ion influx and AMPA receptors allow the passage of Na^+ and K^+ ions. Thus, both of these ionotropic glutamate receptors mediate excitatory neurotransmission, and their activation results in cell membrane depolarization [reviewed by Seeburg (64)].

There are several series of data suggesting an altered glutamatergic neurotransmission in depression [reviewed by Sanacora et al. (65)]. Specifically, it has been shown that glutamate metabolism differs significantly between depressed patients and controls when assessing glutamate and/or glutamine levels in plasma or cerebrospinal fluid and when examining platelet intracellular Ca^{2+} release in response to glutamate stimulation (66 – 70). Furthermore, some of these differences have been resolved by chronic antidepressant treatments (71, 72). Magnetic resonance imaging methods have shown reduced glutamate levels in the anterior cingulate cortex (73, 74), which were returned to normal levels following successful antidepressant treatments (74, 75). Thus, an altered glutamatergic neurotransmission appears to be present, but recent data tend to suggest that NMDA and AMPA receptors could be involved in different ways in the pathophysiology of depression.

Preclinical tests for antidepressant efficacy have shown "antidepressant-like" properties of NMDA-receptor antagonists (76, 77), including functional antagonists and ligands for the glutamate, glycine, polyamine, bivalent cation, and ionophore recognition sites of the NMDA receptor complex (76, 78 – 80). The "antidepressant-like" effects of NMDA antagonists likely involve NMDA receptors located in the hippocampus as the NMDA antagonist 2-amino-7-phosphonoheptanoic acid (AP-7), when injected directly into the hippocampus, decreases immobility time in the forced swimming test (FST) (81).

Conversely, classical antidepressant treatments have been linked to changes in NMDA-receptor properties. For example, antidepressant drugs produce a time- and dose-dependent change in the radioligand binding properties of the NMDA receptor (82 – 91). These changes are present with all antidepressant classes (87) and may involve an alteration in the expression of NMDA-receptor subunits (92, 93). Chronic antidepressant treatments can also alter NMDA-receptor function (94 – 96).

In humans, NMDA-receptor abnormalities have been observed in suicide victims (97). A decrease in the expression of the subunit 1 of the NMDA-receptor mRNA has also been documented in the hippocampus of depressed patients (98). Clinical studies with the NMDA antagonists amantadine, memantine, and ketamine have shown efficacy in depression (99 – 102). Therefore, these data suggest that a dysfunction of the NMDA receptor could be involved in the pathophysiology of major depression and that drugs that modulate NMDA mediated neurotransmission may possess "antidepressant-like" properties.

Recently, AMPA receptors have also been implicated in antidepressant effects, due to the observation that the AMPA receptor potentiator LY392098 possesses "antidepressant-like" properties in the FST and in the tail suspension test. LY392098 alone dose-dependently decreased immobility similarly to classical antidepressants and at sub-threshold doses, significantly increased the potency of other antidepressants (103). In primary neuronal cultures, LY392098 also increased brain derived neurotrophic factor (BDNF) mRNA (104), which is suggested to play a critical role in the action of antidepressants (105 – 107). In addition, treatments with classical antidepressants influence AMPA receptors. Specifically, chronic antidepressant treatments increase the expression of AMPA receptors in hippocampal membranes (108) and increase the phosphorylation of AMPA receptor subunits (109), which may indicate an enhanced AMPA-mediated synaptic transmission.

Alternatively, the involvement of glutamate receptors in antidepressant action may originate from a common downstream effect. For example, a downstream effect of the activation of glutamate receptors is an increase in Ca^{2+} levels and, in turn, of nitric oxide (NO) synthesis (110). NO may be involved in the relationship between antidepressants and glutamate transmission, as a potential role for NO in affective disorders has been proposed (111, 112). Antidepressants can inhibit the activity of neuronal NO synthase (nNOS) (113, 114). Accordingly, NOS inhibitors are active in acute and chronic preclinical antidepressant screening paradigms (115 – 118).

4. Serotonin and depression

Serotonin (5-HT) receptors are made up of at least 14

different subtypes [reviewed by Barnes and Sharp (119)]. The 5-HT_{1A}-receptor subtype is of particular importance in the regulation of 5-HT neurons' activity, as somatodendritic 5-HT_{1A} autoreceptors exert autoregulatory control of the firing activity of 5-HT neurons (120, 121).

In addition to 5-HT_{1A} autoreceptors, high densities of 5-HT_{1A} receptors located postsynaptically are found in the hypothalamus, amygdala, hippocampus, lateral septum, and medial prefrontal cortex (mPFC) (122 – 125). Activation of 5-HT_{1A} receptors by 5-HT or 5-HT_{1A} agonists leads to membrane hyperpolarization and a suppression of the neuronal firing activity (126 – 131). Other 5-HT receptors have also been implicated in depression, but this review will focus on only the 5-HT_{1A} receptors and the effects of antidepressants on this receptor population.

The 5-HT hypothesis of depression originated in the 1960's and proposed that low levels of 5-HT in certain brain receptors led to depression (132). It was then modified to propose that a deficiency in brain 5-HT increased one's vulnerability to depression, as suggested by the observations that interference with the 5-HT system or storage may induce depression in vulnerable individuals and that antidepressants enhance central 5-HT neurotransmission [reviewed by Maes and Meltzer (133)].

Tryptophan depletion studies provided further support for the importance of the 5-HT system in antidepressant activity, but not necessarily in the pathophysiology of depression. In remitted depressed patients receiving selective serotonin reuptake inhibitors (SSRIs), acute L-tryptophan depletion led to a rapid return of depressive symptomatology. However, remitted patients maintained with tricyclics were less prone to relapse following tryptophan depletion (134, 135).

A more recent hypothesis is that a simple deficiency of 5-HT is not the sole cause of depression and that depression likely involves dysfunction in brain areas that are modulated by monoaminergic systems such as the frontal cortex and the hippocampus [reviewed by Delgado and Moreno (136)].

There are convincing lines of evidence suggesting a role of the 5-HT system in the mechanism of action of antidepressants. Overall, electrophysiological studies have demonstrated that all known antidepressants including tricyclics, SSRIs, monoamine oxydase inhibitors (MAOIs), electroconvulsive treatments, and even more selective noradrenegic treatments such as desipramine, reboxetine or mirtazapine, enhance 5-HT neurotransmission following chronic treatments, via different mechanisms (137) (Table 1).

Following acute and short-term treatments, SSRIs, similarly to MAOI's, decrease the firing activity of DRN 5-HT neurons (138 – 140), whereas a chronic administration of these medications leads to a desensitization of 5-HT_{1A} somatodendritic autoreceptors in the DRN (137, 141, 142). The proportion of 5-HT neurons with desensitized autoreceptors was shown to increase progressively during the course of several weeks of SSRI administration (143), and in microdialysis studies, the acute administration of SSRIs produces a small, transient increase in extracellular 5-HT concentration in the rat frontal cortex, while 14-day continuous infusion produced a 6-fold increase (144).

Moreover, 14-day treatments with fluoxetine were shown to result in a selective uncoupling of 5-HT_{1A} receptors from G-proteins in the DRN, but not in the hippocampus (145). However, in the hippocampus, the sensitivity of postsynaptic 5-HT_{1A} receptor-mediated

Table 1. Effects of long-term antidepressant treatments on 5-HT neurotransmission

	Responsiveness of somatodendritic 5-HT_{1A} autoreceptors	Function of terminal 5-HT_{1B} autoreceptors	Function of terminal α_2-adrenergic heteroreceptors	Responsiveness of postsynaptic 5-HT_{1A} receptors	Net effect on 5-HT neurotransmission
SSRI	↓	↓	○	○	↑
MAOI	↓	○	↓	○ or ↓	↑
5-HT_{1A} agonists	↓	○	n.d.	○	↑
TCA	○	○	↓	↑	↑
ECS	○	○	○	↑	↑
Mirtazapine	○	○	↓	○	↑
NRIs	○	○	↓	↑	↑
NK_1 antagonists	↓	n.d.	↓	○	↑
Sigma agonists	n.d.	n.d.	n.d.	n.d.	↑

↓: decrease, ○: no change, n.d.: not determined, ↑: increase. TCA: trycyclic antidepressants, ECS: electroconvulsive treatments, NRIs: noradrenaline reuptake inhibitors. Adapted from ref. 137.

responses is not changed (138, 140, 142, 146). These adaptive changes in 5-HT neurons may explain the delayed enhancement of 5-HT-mediated transmission, consistent with the clinical onset of action of SSRI's (137).

Overall, antidepressants clearly produce adaptive changes in the 5-HT system following chronic treatments. Whether these changes are key to the therapeutic efficacy of antidepressants remains to be determined. It is possible that alterations in 5-HT neurotransmission may just be one step involved. Similarly to what has been proposed for the glutamatergic system's involvement in antidepressant action, a downstream mechanism may also be necessary and therefore a downstream target common to both the glutamatergic and serotonergic systems might be the common target of antidepressant medications. Regardless, changes in 5-HT transmission in electrophysiological and microdialysis models are predictive of antidepressant potential, and therefore, they can be used as indices to assess potential novel antidepressants.

5. Sigma receptors and depression

5.1. Sigma ligands as antidepressants

The first interest in sigma ligands as antidepressants originated from the observation that the antidepressants fluvoxamine, fluoxetine, citalopram, sertraline, clorgyline, and imipramine all possess moderate to high affinity (K_i = 36 – 343 nM) for $sigma_1$ sites (147 – 149). Conversely, antidepressant treatments or modifications of the 5-HT system induced changes in sigma receptors binding properties. Repeated treatments with the tricyclic imipramine (14 days) cause a decrease in the total number of sigma receptor binding sites without affecting the affinity of [^{3}H]DTG binding to sigma sites in the striatum, hippocampus, and cortex of the rat (150). Similar reductions were observed after chronic administration of fluoxetine. The absence of effect of desipramine and the fact that a depletion of brain 5-HT by *para*(4)-chloroamphetamine (p-CPA) blocks the ability of imipramine to decrease DTG binding, suggest that 5-HT transmission may play a role in the regulation of cerebral sigma binding sites in the rat. It has been proposed that certain differences in the clinical effects of various antidepressants may, in part, be explained by their distinct influence on cerebral sigma receptors (150).

More direct evidence of potential antidepressant properties of sigma ligands were obtained from behavioral investigations. Sigma agonists have been then tested in various behavioral tests classically used to predict an antidepressant activity. SA 4503 (151), (+)-pentazocine, DTG, JO-1784, and SKF-10,047 dose-dependently decrease immobility in the FST. These effects were blocked by the sigma antagonist NE-100 or BD1047 (151 – 153) (Fig. 2). In addition, SA 4503 and (+)-pentazocine also decreased immobility time in the Tail Suspension Test, an effect also antagonized by NE-100 (154). Interestingly the antidepressant-like

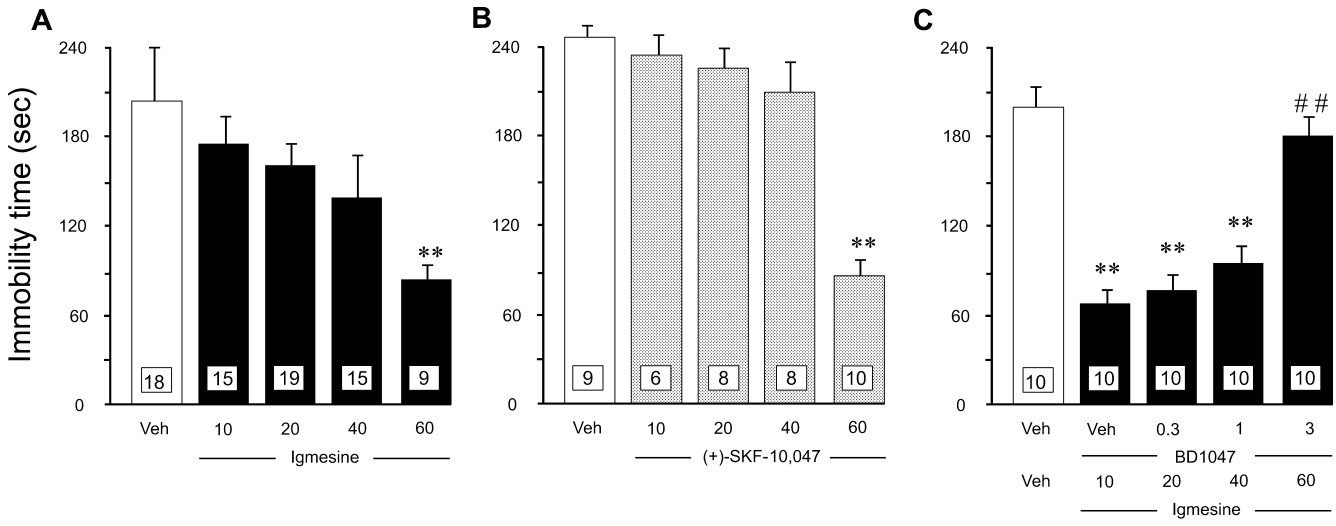

Fig. 2. Antidepressant-like effect of $sigma_1$-receptor ligands in the forced swimming test in Swiss mice: dose-response effect of igmesine (A), (+)-SKF-10,047 (B), and antagonism by BD1047 of the igmesine-induced effect (C). Drugs were injected i.p. 30 min before the session on day 2. BD1047 was administered i.p. 15 min before igmesine, which was given 30 min before the session on day 2. The duration of immobility was recorded for the last 5 min over a 6-min session. Values are expressed as the mean ± S.E.M. of the number of animals indicated inside each column. $^{**}P<0.01$ versus the vehicle-treated group (Veh), $^{\#\#}P<0.01$ versus the igmesine-treated group (Dunnett's test). Adapted from ref. 26.

effect of SA 4503 in the FST was potentiated by the non-competitive NMDA antagonist amantadine (155).

Recently, OPC-14523, a combined sigma$_1$ and 5-HT$_{1A}$ receptor ligand (156), yielded interesting results in the FST (156, 157). Single doses decreased immobility time and the effect of OPC-14523 was enhanced by its daily administration for 7 days. Both the sigma$_1$-receptor antagonist NE-100 and the selective 5-HT$_{1A}$ antagonist WAY 100635 (158) antagonized the behavioural effects of a single dose of OPC-14523 in the FST (157). Moreover, a one-week pretreatment with p-CPA, failed to diminish the antidepressant effects of OPC-14523 in this behavioral test (159), suggesting that sigma receptors alone can mediate the antidepressant effects produced by OPC-14523 and that the combination of the sigma- and 5-HT$_{1A}$-receptor activity could induce a more potent or rapid "antidepressant-like" effect. In keeping with this hypothesis, a potentiation of the "antidepressant-like" effects in the rodent FST has been obtained with the combined administration of sigma and 5-HT$_{1A}$-receptor agonists compared with their separate administration (160). In the chronic mild stress behavioral (CMS) model (chronic stress is believed to be involved in the etiology of affective disorders), the sigma ligands SKF-10,047 and dextrometorphan reversed the motor suppression induced by stress (161, 162).

Most of the data on sigma receptors and depression have focussed on the sigma$_1$ receptor; however, the sigma$_2$ ligand Lu 28-179 also showed "antidepressant-like" activity in the CMS model of depression. Specifically, three-week treatments with antidepressants led to a normalized sucrose intake, which reversed the decreased intake caused by the stress. Lu 28-179 did not affect sucrose intake in non-stressed controls, but produced a significant increase in sucrose intake in rats exposed to CMS (163). However, even if Lu 28-179's has a higher affinity for sigma$_2$ receptors, it also has affinity for sigma$_1$ receptors (164); therefore, a role of the sigma$_1$ receptors in these "antidepressant-like" effects of Lu 28-179 cannot be excluded.

In animal models, neurosteroids with affinity for sigma receptors have also been shown to exert "antidepressant-like" effects that are dependent on the endogenous neurosteroidal systems. For example, in ADX/CX mice, the effect of JO-1784 in the FST was enhanced compared to control animals, whereas another sigma$_1$ agonist, PRE-084 (165), demonstrated a significant antidepressant effect only in ADX/CX mice (26). The sigma$_1$-antagonist BD 10047 (166) blocked all these effects (26). Furthermore, treatments with finasteride, which lead to the accumulation of progesterone, blocked the sigma$_1$-mediated effects. Thus, as discussed previously, circulating steroids appear to exert a tonic modulatory effect on the sigma$_1$ receptor and therefore on sigma$_1$ receptor-mediated "antidepressant-like" effects (26). It has thus been proposed that the potency of sigma$_1$ agonists as antidepressants is highly dependent on the endogenous progesterone levels. Depressed patients such as the elderly with decreased levels of neurosteroids, which would be tonically inhibiting sigma receptors to a lesser degree, might be particularly sensitive to such treatments (26).

Only a few clinical data are available regarding the effect of sigma ligands in depressed patients. In an open study, a small number of depressed patients were treated with JO-1784 which induced a 50% reduction of intensity of the depressive symptoms on the Hamilton depression scale (J.L. Junien and F. Roman, personal communication). Moreover, the only results from a double-blind placebo controlled study, obtained from an interim analysis, showed that a dose of 20 mg/day of JO-1784 was superior to placebo and to 20 mg/day of fluoxetine. However, at 100 mg/day, JO-1784 was not different from the placebo (167), which is in keeping with the bell-shaped dose-response curves mentioned above (167).

Therefore, even if very limited, the clinical data also support the hypothesis that sigma agonists could be effective antidepressant medications. However, the mechanisms of action, through which sigma ligands could exert their antidepressant effects have not been clearly identified.

5.2. Possible mechanisms of action for sigma ligands as antidepressants

5.2.1. Sigma receptors and glutamatergic neurotransmission

Numerous studies have shown interactions between sigma receptors and NMDA-receptormediated responses. For example, sigma ligands, including haloperidol, (+)-pentazocine, 4-IBP (168), (+)-3-PPP, (+)-SKF-10,047, and DTG, antagonize NMDA receptor currents in *Xenopus* oocytes (169). The effect of sigma ligands on NMDA receptors in this study were thought to be indirect; however, high doses (μM) and/or nonselective sigma ligands were used. Furthermore, there was no correlation between the potency of NMDA-receptor inhibition and the affinity or stereoselectivity for sigma sites (169 – 171). Thus, it is difficult to assess whether these observations were based on sigma-receptor-mediated actions rather than on non-specific effects. More recently, in vitro radioligand binding studies showed that haloperidol, (+)-pentazocine, DTG, (+)-SKF-10,047, and (+)-3-PPP inhibited [^{3}H]TCP binding to NMDA receptors in neuronal cells, with a potency

correlated with the affinity for DTG binding sites (172, 173).

In our laboratory's model of modulation of the NMDA response in dorsal hippocampal pyramidal neurons of the CA_3 region, it was found that low doses of the sigma ligands DTG, JO-1784, (+)-pentazocine, and L-687,384 selectively potentiated the response of these neurons to microiontophoretic applications of NMDA (29, 32, 33, 35, 51). Other sigma ligands like BD-737, 4-IBP, and OPC-14523 were less selective as they also modulate quisqualate (QUIS)-induced response (29, 174) (JE. Bermack and G. Debonnel, unpublished observation). Interestingly, it was also found that depending on the initial level of excitatory response to QUIS and NMDA, sigma agonists could increase or decrease the NMDA- and QUIS-induced responses, thus suggesting a real modulatory role of sigma ligands on the glutamatergic response (174) (JE. Bermack and G. Debonnel, unpublished observation). The potentiation induced by these sigma agonists was suppressed by antagonists such as BMY-14802, (+)-3-PPP, and NE-100 (29, 32, 33, 35). The effects of all $sigma_1$ agonists on the NMDA response produced a bell-shaped dose-response curve, as previously described (29, 175). As stated above, this particular pharmacological profile could explain the discrepancies observed for the effects of sigma ligands with respect to inhibition versus potentiation on NMDA-receptor-mediated responses, as most in vitro studies may have used high doses, at which the sigma ligands were acting as antagonists.

Interestingly, in the model of the modulation of the NMDA response in the dorsal hippocampus, the antidepressants sertraline and clorgyline with a high affinity for $sigma_1$ receptors potentiate the NMDA response. In contrast, the antidepressants paroxetine and tranylcypromine with low affinity for sigma receptors had no effects on the NMDA response despite their similar monoaminergic profiles to sertraline and clorgyline, respectively. Moreover, the effects of sertraline and clorgyline were suppressed by the sigma antagonist haloperidol but not by spiperone, suggesting that they were likely mediated by sigma receptors (35).

The $sigma_2$ ligands Lu 28-179 (176) and BD-1008 (177) have also been shown to modulate NMDA-mediated responses. Despite their high affinity for $sigma_2$ receptors, the doses required were, however, 5-10 times higher than $sigma_1$ ligands (178). The effects of Lu 28-179 were not blocked by the $sigma_1$ antagonists NE-100, progesterone, or haloperidol, suggesting that these effects were mediated through $sigma_2$ receptors (178).

In vitro models have also suggested a modulatory role for $sigma_1$ agonists on NMDA-mediated responses. For example, JO-1784, BD-737, (+)-pentazocine, and (+)-3-PPP potentiated in a concentration-dependent manner NMDA-induced [^{3}H]NE release from preloaded rat hippocampal slices (30, 51, 179), whereas DTG and BD-737 acted as inverse agonists, by concentration-dependently inhibiting the overflow of [^{3}H]NE evoked by NMDA. Haloperidol and BD-1063 (166) alone did not modify [^{3}H]NE release, but completely prevented the effects of JO-1784, BD-737, (+)-pentazocine, DTG, and (+)-3-PPP (30, 51, 179), whereas DuP734 inhibited that of BD-737 (180).

Neurosteroids acting as sigma agonists have also been shown to modulate NMDA-receptor-mediated effects, as DHEA at low doses potentiates the NMDA response in extracellular recordings from the dorsal hippocampus. The effect of DHEA was blocked by NE-100 and haloperidol (25). In this model, neither pregnenolone nor pregnenolone sulfate modified the NMDA response or acted as antagonists, which may be due to their lower affinity for $sigma_1$ receptors (13, 22). In this model, both progesterone and testosterone act as antagonists and suppress the potentiation of the NMDA response induced by sigma agonists such as DTG, (+)-pentazocine, and JO-1784. DHEA's response is blocked by pertussis toxin, while progesterone's is not, suggesting again that different $sigma_1$ subtypes may be involved in the modulation of the NMDA response by neurosteroids (25, 181).

Neurosteroids are also active in the in vitro model of NMDA-induced [^{3}H]NE release from hippocampal slices. Specifically DHEAS potentiates while pregnenolone sulfate inhibits (inverse agonist effect) NE release (179). Both effects are blocked by haloperidol, progesterone, BD-1063, and by a pertussis toxin pretreatment, suggesting G-protein-dependent $sigma_1$ receptors are responsible (179).

Furthermore, endogenous hormone levels affect the sigma receptor's modulatory effect on NMDA-mediated responses. For example, 2 weeks following OVX, the potentiation of the NMDA response induced by DTG was significantly greater than in control female rats, suggesting that sigma receptors may be tonically inhibited by endogenous progesterone (24, 181). In agreement, 10 times higher doses of (+)-pentazocine and DHEA were required in pregnant females to potentiate the NMDA response. This reduced effect of sigma agonists in late pregnancy may be due to occupation of sigma receptors by high levels of progesterone, which also supports its potential role as an endogenous ligand for $sigma_1$ receptors (24, 181).

In keeping with the hypothesis of progesterone endogenously binding to sigma receptors, during the post-partum period, the degree of potentiation of the

NMDA response by DTG, (+)-pentazocine, and DHEA was significantly higher than that observed in control females, and at Days 10 – 15, the potentiation of the NMDA response returned to control values. This apparent supersensitivity of sigma receptors observed during the post-partum period might be due to the rapid drop of progesterone levels after delivery (182, 183). In keeping with these data, in OVX rats treated for 3 weeks with progesterone (1000 μg kg^{-1} day^{-1}), low doses of DTG, JO-1784, DHEA, or (+)-pentazocine did not induce any potentiation of the NMDA response. The potentiation by these ligands returned to normal after a 5-day washout (25). The necessity of such a long washout before the NMDA response returns to normal following progesterone treatments would suggest that long lasting adaptive change in sigma receptors could be involved, following long-term treatments with sigma antagonists.

Overall, many sigma ligands have demonstrated the ability to modulate NMDA-mediated glutamatergic neurotransmission. Since NMDA receptors may be involved in the mechanism of action of antidepressants and as an altered glutamatergic neurotransmission may underlie depressive pathology, the ability of sigma receptors to modulate NMDA-receptor-mediated responses may have important implications towards the potential of sigma ligands as antidepressants.

To test this hypothesis, we investigated the effects of treatments with sigma ligands on NMDA receptor-mediated behaviors at three weeks after an olfactory bulbectomy (OBX), an established animal model of depression (83, 184, 185), which induces a decrease in NMDA receptor ligand binding (186). Treatments with sigma ligands were able to reverse the effects of OBX surgery on NMDA receptor-mediated behaviors. The effects of the sigma ligands tested were dependent on the dose administered and on the duration of the treatments. The effects of the different doses were in keeping with the bell-shaped dose-response curve previously reported for these sigma ligands. Importantly, this behavioral study clearly suggests a potential for sigma ligands as antidepressants in a dose- and duration-dependent manner, as treatments with sigma ligand can reverse OBX-induced NMDA-mediated behaviors.

5.2.2. Sigma receptors and serotonergic neurotransmission

When examining potential novel antidepressants, one cannot exclude the involvement of the 5-HT system. As stated above, 5-HT plays a key role in depression and/or the mechanism of action of antidepressants. Thus, it begs the question, when examining sigma ligands' potential as antidepressants, whether they can modulate 5-HT neurotransmission.

Previous experiments had provided controversial evidence regarding possible interactions between sigma receptors and the 5-HT system. Peripheral 5-HT-sigma interactions have been proposed, as DTG, haloperidol, and BMY-14802 have been found to inhibit the 5-HT-evoked contractions of the guinea pig ileum longitudinal muscle/myenteric plexus preparation in a manner showing high correlation with their potency to compete with DTG binding (187). However, in a behavioral study, the sigma ligand EMD 57445 did not affect several 5-HT related parameters such as 8-OH-DPAT-induced behavioural syndrome, *m*-chlorophenylpiperazine-induced hypothermia or L-5-hydroxytryptophan-induced head twitches (188). In addition, biochemical studies showed that EMD 57445 and the sigma$_1$ ligand PD144418 did not induce any change in 5-HT or 5-hydroxyindoleacetic acid (5-HIAA) levels in various brain regions, suggesting that these ligands exert no effects on 5-HT-receptor populations or 5-HT metabolism (188, 189). However, EMD 57445 and PD 144415 have been suggested to be a sigma antagonists and therefore may have no effects on their own.

To investigate whether sigma ligands can modulate 5-HT neuronal activity in vivo we examined the effects of short- and long-term administration of various sigma ligands on 5-HT basal neuronal activity in the DRN, using extracellular recordings. As stated above, acute treatments with SSRIs and MAOIs induce a decrease in the firing activity of DRN 5-HT neurons (138, 139, 190). However, after long-term treatments, there is a restoration of the firing activity of these neurons (138, 139, 191, 192) due to the desensitization of the 5-HT$_{1A}$ autoreceptors (137, 141, 142). This paradigm of recordings from 5-HT neurons provided an ideal model to study sigma ligands' effect in a manner with which the results could be easily compared to those obtained with classical antidepressants.

In contrast with what has been observed in the dorsal hippocampus, the acute intravenous administration of (+)-pentazocine had no effect in the dorsal raphe. Interestingly, however, we found that the sigma ligands 4-IBP, (+)-pentazocine, and DTG after either 2 or 21 days of treatment induced a significant effect on the firing activity of 5-HT neurons of the DRN, which was increased by more than 50% (193) (Fig. 3). These findings suggest a clear modulation of 5-HT neurotransmission by sigma ligands in vivo, a novel finding with respect to sigma receptor research, supporting a role for sigma receptors in depression. They also suggested that sigma ligands modulate 5-HT neurotransmission by a mechanism different from those of classical antidepressants, as they induced an increase in

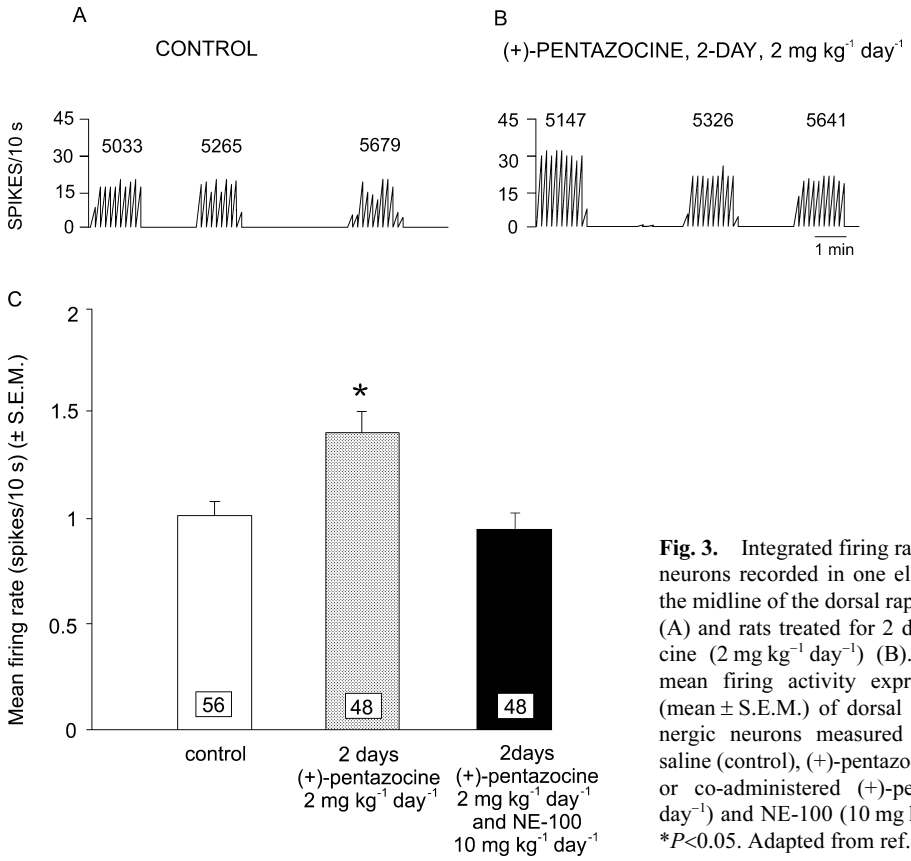

Fig. 3. Integrated firing rate histograms of 5-HT neurons recorded in one electrode descent along the midline of the dorsal raphe nucleus in controls (A) and rats treated for 2 days with (+)-pentazocine (2 mg kg^{-1} day^{-1}) (B). Panel C shows the mean firing activity expressed as spikes/10 s (mean ± S.E.M.) of dorsal raphe nucleus serotonergic neurons measured in rats treated with saline (control), (+)-pentazocine (2 mg kg^{-1} day^{-1}), or co-administered (+)-pentazocine (2 mg kg^{-1} day^{-1}) and NE-100 (10 mg kg^{-1} day^{-1}) for 2 days. *P<0.05. Adapted from ref. 193.

the firing activity of 5-HT neurons after only 2 days of treatment. If one accepts the hypothesis that the firing activity of 5-HT neurons represents a direct index of the efficacy of the 5-HT neurotransmission, this suggests that sigma ligands may represent antidepressants with a fast onset of action. Further studies were also conducted with the $sigma_1$ ligand OPC-14523, which also presents high affinity for the 5-HT_{1A} receptor and moderate 5-HT reuptake blocking activity (156, 157). OPC-14523, similarly to other sigma ligands, induced a significant increase in the firing activity of 5-HT neurons of the DRN after 2 days of treatment. This increase in the firing activity was blocked by the coadministration of NE-100, suggesting that it was mediated by $sigma_1$ receptors. Interestingly, in addition, OPC-14523 after a 2-day treatment induced a decrease in the responsiveness of the 5-HT_{1A} autoreceptor (194). This is particularly significant given that classical antidepressant medications require chronic treatment for this decreased autoreceptor response to occur (138, 141, 142). If present with other $sigma_1$ agonists, this rapid desensitization of the 5-HT_{1A} autoreceptor, in addition to the observed rapid increase in the firing activity of 5-HT neurons after only 2 days of treatment, would constitute another argument to suggest that sigma agonists have potential to produce a fast onset of antidepressant effect.

In keeping with the data obtained with sigma agonists, recent electrophysiological studies in the rat have shown that if progesterone does not have any effect by itself on 5-HT neuronal activity in the DRN, several of its metabolites such as alloprenanolone or other neurosteroids such as DHEA increase the firing activity of DRN 5-HT neurons, similarly to what is observed during pregnancy in correlation with the increase in progesterone level. Interestingly, at least part of these effects of neurosteroids are mediated through an activation of sigma receptors as they are reversed by NE-100 (195).

The precise mechanisms through which sigma ligands increase the firing activity of DRN 5-HT neurons is not established. One possibility is that this effect is mediated locally, in the DRN, as a consequence of the modulation of the glutamatergic neurotransmission as AMPA and NMDA receptors have been shown to mediate the glutamatergic excitatory input in the DRN (196). However, this effect could be also an indirect one; specifically, treatments with sigma ligands may rapidly modulate NMDA receptor-mediated transmission in the hippocampus, and potentially other forebrain regions, which in turn would lead to a modulation of 5-HT neurotransmission in the DRN via feedback loops to

DRN 5-HT neurons. Indeed, an afferent connection has been identified that projects from the hippocampus to the DRN via the lateral habenula (197 – 201).

Another feedback loop that may be involved is the "long feedback loop" that projects from the DRN to mPFC and back to the DRN (196, 199, 202 – 206). Therefore, the activity of the DRN neurons is dependent on the balance between the excitatory input from various brain regions (e.g., lateral habenula and mPFC) and inhibitory input from GABAergic interneurons in distal areas (e.g., periaqueductal gray area) and local GABAergic interneurons situated in the DRN (201, 207 – 209).

Such an indirect effect might explain the delayed onset of action of sigma ligands in the electrophysiological paradigm of DRN 5-HT neurons. It is possible that sustained treatments are leading to a potentiation of NMDA-receptor-mediated responses in the mPFC and/or other brain regions in addition to the hippocampus. This could cause an increase in the excitatory input from the mPFC to the DRN, which at some point may overcome the GABAergic inhibitory influences and shift the balance controlling the activity of the 5-HT neurons of the DRN, leading to an overall net increase in DRN 5-HT neuronal activity. This theory could explain why chronic treatments are needed for any alterations to be observed in the DRN, but not in the hippocampus.

Another factor likely contributing to the requirement of a sustained treatment to observe an effect is based on the density of sigma receptors at the plasma membrane, which is progressively altered by the presence of sigma ligands. This was shown in cell lines in which treatments with sigma agonists induced an increase in the sigma receptor density at the plasma membrane, following a minimum of 2 days of treatment (210). Thus, as treatments with sigma ligands continue and sigma receptors density increased in the plasma membrane, they can exert more significant effects on NMDA-receptor-mediated signalling. Based on this hypothesis, sigma receptors would also be increasing in concentration in DRN neuronal plasma membranes so that a stronger modulation of NMDA-receptor-mediated signalling occurs.

5.2.3. Sigma receptors and Ca^{2+} regulation

Attempts to identify the mechanisms by which sigma ligands exert their "antidepressant-like" properties have also linked these aspects to sigma receptors' regulation of Ca^{2+}. The effects of JO-1784 in the FST were demonstrated to be Ca^{2+}-dependent as the extracellular Ca^{2+} chelator EGTA prevented the effect of JO-1784 in a dose-dependent manner. In addition, a lower dose of JO-1784 had no effect by itself, but co-administered with the L-type voltage-dependent Ca^{2+} channel (VDCC) positive modulator (–)-Bay K8644, it significantly reduced immobility. In agreement, the L-type VDCC antagonist verapamil and the N-type VDCC antagonist ω-conotoxin blocked the effects of JO-1784 (211). Therefore, $sigma_1$ receptors may be interacting with pre- or postsynaptic VDCC's to exert "antidepressant-like" effects in the FST (211).

In addition, bradykinin, which increases IP_3 levels, enhanced the effect of JO-1784 (211), whereas the IP_3-receptor antagonist xestospongin C blocked the effect of JO-1784. Thus the mobilization of intracellular Ca^{2+} from IP_3 receptor-sensitive pools appears also to participate initially in the behavioral effects mediated by $sigma_1$ receptors located on the ER membranes (211). The $sigma_1$ receptor then putatively moves to the plasma membrane and interacts with VDCC's (31, 60).

It is likely that sigma ligands' ability to modulate both glutamatergic and 5-HT transmissions contribute to the "antidepressant-like" effects observed in behavioral models. The molecular mechanism underlying sigma receptors' ability to modulate 5-HT and glutamatergic transmissions may involve sigma receptors' ability to modulate Ca^{2+} (31, 58, 60, 212) or K^+ signalling (43, 50, 54, 213). This modulation could represent a downstream target involved in the effects of sigma ligands on both the glutamatergic and the 5-HT systems, thus leading to one primary target. The effect of antidepressants on downstream targets has been a recent and important shift in antidepressant research. As reviewed by recent literature, downstream targets are the focus for a mechanism of action for antidepressants and downstream adaptive changes could explain the time lag seen between changes in neurotransmitter systems and therapeutic effects seen in patients (reviewed by refs. 106 and 214 – 216). However, besides Ca^{2+} regulations, one downstream target of particular interest for antidepressant treatments is represented by neurotrophic factors (reviewed by refs. 106, 107, and 214 – 216).

5.2.4. Sigma receptors and neurogenesis

Recent evidence has shown an hippocampal atrophy in major depression, which can persist long after the pathology is resolved (217 – 220). This atrophy could be due to a regression of dendritic processes, an inhibition of neurogeneration or the loss of hippocampal neurons [reviewed by Sapolsky (221)]. It has also been shown that hippocampal atrophy can be reversed by successful antidepressant treatments and that in vitro, classical antidepressants promote neurogenesis (222). A recent study has provided a role for $sigma_1$ receptors in cell morphological changes, specifically in the initiation of neurite outgrowth and sprouting (210, 223). $Sigma_1$ receptors

and ankyrins are highly concentrated in the growth cone of NG-108 cells, a region related to neurite sprouting, extension, and guidance (223). The $sigma_1$ agonist (+)-pentazocine had no effect by itself on neurite sprouting, but potentiated the neurite-sprouting induced by nerve growth factor (NGF) (210). In contrast, neurite sprouting induced by cAMP in PC12 cells was not affected by (+)-pentazocine. The $sigma_1$ antagonist NE-100, regardless of the presence of NGF, did not affect neurite sprouting, but antagonized the potentiation induced by (+)-pentazocine, thus clearly indicating a mediation via $sigma_1$ receptors (210).

Interestingly, similar to sigma agonists, the antidepressants imipramine and fluvoxamine potentiated the effects of NGF in this model (210). These effects of imipramine and fluvoxamine were antagonized by NE-100, while no concentration of 5-HT tested affected neurite sprouting induced by NGF (210), therefore suggesting that the effect on NGF-induced neurite outgrowth of both $sigma_1$ agonists and classical antidepressants are mediated by $sigma_1$ receptors. Moreover, cell treatments with NGF, even in the absence of $sigma_1$-receptor agonists, increased the level of $sigma_1$ receptors in a dose-dependent manner, and the effects of (+)-pentazocine and NGF were additive (210). Interestingly, treatment with imipramine and fluvoxamine also increased $sigma_1$ receptors. Furthermore, in MT40 cells expressing higher levels of $sigma_1$ receptors, NGF was found to be more potent in inducing neurite sprouting, whereas treatments with $sigma_1$-receptor antisense significantly reduced the degree of neurite sprouting (210). Together, these data suggest a primary role for $sigma_1$ ligands in enhancing NGF-induced neurite growth.

One member of the neurotrophin family, BDNF, has been heavily implicated in the action of antidepressants, as chronic treatments with a variety of antidepressant therapies induce an increase in BDNF expression (224 – 226). Moreover, BDNF administration itself has been shown to produce antidepressant effects in behavioural models of depression (227, 228).

It would be interesting to know the effects of sigma ligands on BDNF. Thus far, this has only been studied with the sigma ligand E-5842, which showed no effects on BDNF or NGF levels following chronic treatments (229). However, again, E-5842 presents a sigma antagonist profile, so its lack of efficacy cannot be considered as an indication of what might be the effects generated by sigma agonists. It is still conceivable that sigma agonist would potentiate the effects of BDNF, similarly to that observed previously with NGF.

Another growth factor is the epidermal growth factor (EGF). EGF is present in the CNS and known to stimulate cell proliferation. A recent report from the group of Su indicated that in PC_{12} cells, the overexpression of $sigma_1$ receptors induced a 3-fold increase of neurite sprouting, which was suppressed by the $sigma_1$ antagonist NE-100 (230). In the context of this review, these data are even more interesting if one considers that EGF has been shown to enhance NMDA-induced modulation of intracellular Ca^{2+} (231).

More research will be required to elucidate the exact basis for the observed potentiation of neurotrophin effects by sigma agonists and whether sigma ligands always affect neuronal survival and neurogenesis. From there, it would be interesting to see whether these effects are necessary for the observed modulatory effects of sigma receptors on many neurotransmitter systems. This will provide many new avenues to explore the field of sigma receptors and offer valuable information about the clinical potential of these ligands.

6. Conclusions

The glutamatergic and serotonergic systems are heavily implicated in antidepressant action. $Sigma_1$ ligands have demonstrated “antidepressant-like” effects in animal models screening for antidepressant action. Moreover, $sigma_1$ ligands have been shown to modulate glutamatergic and serotonergic neuronal activity in in vivo electrophysiological paradigms. These actions of $sigma_1$ ligands suggest that $sigma_1$ ligands may have potential as novel antidepressant agents. Furthermore, the data also suggests that $sigma_1$ ligands may present a novel mechanism of antidepressant action with potential for a faster onset of action versus classical antidepressants. Therefore, the data presented in the current Review strongly support the further investigation into $sigma_1$ ligands as potential antidepressants.

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