Current Hypotheses on Sigma Receptors and their Physiological Role: Possible Implications in Psychiatry

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During the last years, due to the availability of selective ligands, numerous investigations have been dedicated to sigma receptors. The existence of different subtypes of these receptors is now accepted; their endogenous ligand has not yet been identlfied, but some candidates have been proposed. Evidence suggests that one of their major roles might be to regulate the activity of the glutamatergic system via the *N*-methyl-D-aspartate receptor. The potential involvement of sigma receptors in psychiatry was suggested by the psychotomimetic effects of their earliest ligands and the fact that several neuroleptics have a high affinity for them. Recently, new arguments have strengthened this hypothesis: some molecules with high sigma affinity but low dopaminergic affinity display a "neuroleptic-like" pharmacological profile; post-mortem studies have shown a reduction of sigma binding sites in the brain of patients with schizophrenia; cocaine, which can induce psychotic episodes, has high affinity for sigma receptors. Hence, by modulating the glutamatergic inputs, by regulating directly the firing activity of dopaminergic neurons, or by both mechanisms, sigma receptors could be involved in the pathophysiology and/or in the treatment of schizophrenia.

Key Words: schizophrenia, sigma, neuropeptide Y, NMDA (*N*-methyl-D-aspartate), glutamate

INTRODUCTION

After more than three decades of near stagnation, the last few years have witnessed the eclosion of new developments which may be of great importance to the understanding and the treatment of schizophrenia. Several new atypical neuroleptics have been commercialized in North America and Europe or will be approved soon (Meltzer et al 1989a; 1989b; Farde et al 1989; Snyder and Largent 1989; Deutch et al 1991). The fact that these neuroleptics are clinically active without inducing extrapyramidal symptoms or tardive dyskinesia casts some doubt on the long-standing dopaminergic hypothesis of schizophrenia, which postulates that the antipsychotic effect of neuroleptics is solely attributable to the blockade of D_2 dopaminergic post-synaptic receptors. Indeed, beside the classical D_1, and D_2 dopaminergic receptors, three new subtypes of dopaminergic receptors (D_3, D_4 and D_5) were recently cloned (Snyder 1990; Sokoloff et al 1990; Sunahara et al 1991; Van Tol et al 1991). Moreover, the precise mechanisms whereby these neuroleptics (novel and classical) exert their antipsychotic effects have been addressed from new perspectives. Some innovative explanations have been proposed, such as the implication of other neurotransmitters or the importance of the ratio of the respective affinities of some new neuroleptics for dopaminergic and 5-HT_2, 5-HT_3 or muscarinic receptors, in regard of their clinical efficacy (Meltzer 1989; Meltzer et al 1989b; Snyder and Largent 1989; Abbott 1990; Drescher et al 1990; Seeman 1990; Deutch et al 1991). Finally, an entirely novel approach has been opened with the perspective of the possible implication of sigma receptors in schizophrenia and in the mechanism of action of antipsychotic drugs.

The existence of sigma receptors was first reported by Martin et al, in 1976, who initially classified them as belong-

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ing to the opiate receptor family. The racemic form of the prototypal ligand for these binding sites, the benzomorphan SKF 10,047 (*N*-allyl-normetazocine), similarly to other opiate benzomorphans such as cyclazocine, was an effective analgesic but was found to induce delusions, hallucinations, depersonalization and dysphoria (Haertzen 1970; Brady et al 1982; Shearman and Herz 1982; Shannon 1983). This pharmacological profile prompted numerous studies, but the lack of a clear definition for the sigma binding sites and the absence of selective ligands resulted in much confusion for several years. It was finally accepted that the racemic form of SKF 10,047 was binding to at least three sites (Martin et al 1984). (-)SKF 10,047, responsible for the analgesic effect, acted on the classical μ and kappa opiates receptors (Su 1982; Martin et al 1984), whereas the sigma and phencyclidine (PCP) binding sites, representing the high- and low-affinity sites respectively for (+)SKF 10,047, were assumed to mediate the psychotomimetic effects of the drug (Su 1982; Khazan et al 1984; Mickelson and Lahti 1984; Mickelson and Lahti 1985). Since these latter effects were insensitive to the opiate antagonists naloxone and naltrexone, it was concluded that sigma receptors do not belong to the opiate family (Su 1982; Tam 1983; Vaulpel 1983). The distinction between sigma and PCP binding sites was more difficult to establish and these two receptors were long believed to be similar (Quirion et al 1981). Only in 1987 was the consensus reached that these were two distinct types of receptors (Quirion et al 1987).

Phencyclidine was developed as a general anesthetic but, because of its secondary effects, was withdrawn from clinical use and rapidly became a street drug denoted "angel dust," and is still widely used by drug addicts. PCP induces in normal humans, similarly to (+)SKF 10,047, severe psychodysleptic symptoms resembling those of schizophrenia (Allen and Young 1978). Moreover, in patients with schizophrenia, this drug induces a worsening of the symptomatology lasting as long as several weeks (Luby et al 1959). The mechanisms whereby PCP exerts its effects are now better understood.

Several excitatory dicarboxylic amino acids are present in the mammalian brain. Some of them acting as neurotransmitters or neuromodulators. Curtis and Watkins (1960; 1963) were the first to report that glutamate (GLU), the prototypal excitatory dicarboxylic amino acid, induced an activation when applied locally on spinal neurons and could also induce seizures and neuronal degeneration in different regions of the brain; (Olney 1969; Arees and Mayer 1970). These excitatory and neurotoxic properties of GLU are shared by the other dicarboxylic amino acids, which exert their neuronal excitatory effect by activating three glutamate receptor subtypes, labelled according to their most effective agonist: kainate (KA), quisqualate (QUIS) and *N*-methyl-D-aspartate (NMDA) (Watkins and Evans 1981; Foster and Fagg 1984). The first two would activate a cationic channel in a voltage-independent manner and mediate most of the fast synaptic responses to the excitatory amino acids (Cotman and Monaghan 1987), while the NMDA receptor would be activated mainly in special conditions, to modify the synaptic function. For example, the NMDA receptor mediates the "long-term potentiation," which corresponds to an enhanced response following a high-frequency stimulation (Bliss and Lomo 1973; Collingridge et al 1983a; 1983b; Collingridge and Bliss 1987). Such a mechanism, which has been shown to be involved in learning and memory, can last for several months and may entail some of the morphological changes found in the brain of patients with schizophrenia (Etienne and Baudry 1987).

The NMDA receptor is a "complex" unit including a cationic ion channel associated to several binding sites (NMDA, PCP, glycine, polyamines, magnesium and zinc). NMDA-induced effects are allosterically modulated by glycine, polyamines and Zn^{2+} ions, whereas PCP and Mg^{2+}, whose binding sites located inside the cationic channel antagonize non-competitively the response to NMDA (Mayer et al 1984; Nowak et al 1984; Johnson and Ascher 1987; Snell et al 1987; Ascher 1988; Huettner and Bean 1988; Carter et al 1989; Christine and Choi 1990; Dana et al 1991). It is believed that this non-competitive antagonism of the effect of NMDA is responsible for the psychotomimetic effects of PCP, since similar symptoms have been observed with other non-competitive NMDA antagonists (Zukin and Zukin 1979; Willets and Blaster 1988; Marquis et al 1989).

Beside the psychotomimetic effects of PCP and benzomorphans, the interest in sigma receptors in psychiatry grew in 1982, when it was first demonstrated that the butyrophenone haloperidol has a very high affinity for sigma receptors (Largent et al 1984; Tam and Cook 1984). Indeed, it was shown that the affinity of haloperidol for sigma receptors is equal or greater than its affinity for dopaminergic binding sites (Tam and Cook 1984; Bowen et al 1990a). Moreover, sigma receptors represent more than 50% of the binding sites of [^{3}H]haloperidol, either *in vivo* or *in vitro* (Tam and Cook 1984; Weissman et al 1990). For several years, haloperidol was the ligand with the highest affinity for sigma receptors. Since haloperidol has no affinity for PCP binding sites (Tam and Cook 1984), it has been used in most of the radioligand binding studies of sigma receptors in the presence of spiperone to mask the dopaminergic binding. Several other neuroleptics such as trifluoperazine, molindone, pimozide, chlorpromazine, fluspirilene and thioridazide (Tam and Cook 1984; Deutsch et al 1988; Walker et al 1990; Contreras et al 1990b) also have a high to moderate affinity for sigma receptors. Moreover, some molecules with a high affinity for sigma receptors but a low affinity for dopaminergic receptors display, in animal models, a "neuroleptic-like" pharmacological profile or have been reported in clinical studies to have antipsychotic activity (Ferris et al 1986; Su 1986; Taylor and Dekleva 1987; 1988; Largent et al 1988; Taylor et al 1989). These findings suggest that sigma binding sites may be involved in the pathophysiology and/or in the treatment of schizophrenia. However,

since most of the earliest sigma ligands possessed an affinity for both sigma and PCP receptors, a clear distinction between the physiological role of these two receptors has been long to establish, and it is only in recent years that new data obtained with more selective ligands have provided a better knowlege of sigma receptors.

Localization of sigma receptors

Sigma binding sites have been found in several peripheral tissues, such as the liver, spleen, gastrointestinal tract, adrenal, testis and ovaries (Roman et al 1989; Wolfe et al 1989; Walker et al 1990), but are particularly abundant in the central nervous system, where an heterogenous regional distribution has been found. Autoradiographic studies have revealed high concentrations of sigma receptors in two regions which have been implicated in the pathophysiology of schizophrenia: the substantia nigra (A9) and the limbic system. The more precise description of the meso-limbic and meso-cortical dopaminergic pathways (Ungerstedt 1971; Lindvall and Bjorklund 1974) and the finding that antipsychotic drugs were dopaminergic antagonists (Carlsson and Lindqvist 1963; Van Rossum 1966; Seeman et al 1976; Burt et al 1977; Snyder and Largent 1989) led to the hypothesis that A9 and the ventral tegmental area (A10), which are the two regions from which the dopaminergic system projects to the limbic system and the striatum, may be areas of particular importance in schizophrenia. The pars compacta of A9 was reported to be particularly enriched in sigma receptors labelled with the selective high affinity sigma ligand [^{3}H]1,3-di(2-tolyl)guanidine (DTG) (Gundlach et al 1986; Weber et al 1986; McLean and Weber 1988; Graybiel et al 1989; Walker et al 1990).

The areas of projection of the dopaminergic system have also been implicated in the pathophysiology of this illness. Most of these areas, such as the frontal cortex, and the limbic system have high densities of sigma receptors (Weissman et al 1988; Mash and Zabetian 1992). In the last decade, several post-mortem studies have documented morphological abnormalities in the hippocampal region (a part of the limbic system) in patients with schizophrenia (Kovelman and Scheibel 1984; Christison et al 1989; Jeste and Lohr 1989; Altshuler et al 1990; Heckers et al 1990; Okada et al 1991; Weinberger 1991). The hippocampus is the brain structure which has one of the highest density of sigma receptors in rats (Largent et al 1986; Contreras et al 1987b; McLean and Weber 1988). However, in humans, the density of sigma receptors labelled with [^{3}H]DTG is lower in the hippocampus than in the pars compacta of the substantia nigra (Jansen et al 1991). Interestingly, in the hippocampus, sigma receptors appear to be located mainly on pyramidal neurons (Gundlach et al 1986). Moreover, high densities of sigma receptors have also been found in areas linked to movement control (the cerebellum, the red nucleus and the spinal cord) and in other areas such as the pons, the medulla, the midbrain central grey and the pineal gland (Gundlach et al 1986; Contreras et al 1987b; McLean and Weber 1988; Abreu and Sugden 1990; Barnes et al 1992).

Physiological effects of sigma receptors

Since 1976, numerous effects of sigma ligands have been described. However, it is not yet been clearly established that all of these effects can be attributed solely to the activation of sigma receptors. The use of large doses of ligands, such as (+)SKF 10,047, having an affinity for both sigma and PCP binding sites, produced conflicting results in several cases. Paradoxically, several researchers described "sigma effects," recognizing that these effects were correlated with the affinity of the ligands for PCP but not for sigma receptors (Anis et al 1983; Aanonsen and Wilcox 1987; Lodge et al 1988; Malouf et al 1988a; 1988b; Martin and Lodge 1988; Aram et al 1989; Holtzman 1989; McCann et al 1989; Sagratella et al 1989; Jones et al 1990; Singh et al 1990).

In an attempt to distinguish between the effects of PCP and sigma ligands, several selective high-affinity sigma ligands have been tested in anesthetized rats. An *in vivo* electrophysiological paradigm was used to obtain unitary extracellular recordings from pyramidal neurons of the CA_3 region of the dorsal hippocampus and to assess modifications of their response to microiontophoretic applications of excitatory dicarboxylic amino acids. This region was chosen because it possesses high concentrations not only of sigma receptors, but also of the different types of receptors involved (i.e., NMDA, PCP, KA, QUIS) (Foster et al 1981; Quirion et al 1981; Zukin and Sircar 1985; Cotman and Monaghan 1987; Jarvis et al 1987). This model was used to measure the effect of several sigma ligands on the neuronal firing activity by comparing the responsiveness to microiontophoretic applications of the excitatory amino acids NMDA, QUIS and KA before and after the systemic administration or microiontophoretic application of sigma ligands.

It was found that the intravenous administration of very low doses (0.5 to 3 μg/kg) of the high-affinity sigma ligand DTG does not affect the spontaneous firing activity of CA_3 pyramidal neurons, but produces a marked dose-dependent potentiation of NMDA-induced firing activity. DTG has no effect on KA- and QUIS-induced activations (Monnet et al 1990). A similar potentiation of the response to NMDA was observed with several other high-affinity sigma ligands, such as (+)pentazocine and JO-1784 (Debonnel et al 1990a). However, the intravenous administration of low doses of the three other sigma ligands, haloperidol, BMY-14802 and (+)3-PPP (Largent et al 1984; Taylor and Dekleva 1987) does not modify NMDA-induced firing activity but prevents and reverses the effects of the above-mentioned sigma agonists (Monnet et al 1992c).

To verify that the blockade by haloperidol, BMY-14802 or (+)3-PPP of the enhancement of the response to NMDA by DTG was mediated by sigma receptors and could not be

attributed to an effect on dopaminergic receptors, spiperone, another butyrophenone with a high affinity for dopaminergic receptors but with a low affinity for sigma receptors (Tam and Cook 1984; Weber et al 1986; Taylor and Dekleva 1988), was tested in the same paradigm. Spiperone failed to reverse the potentiation of NMDA-induced activation by the sigma agonists (Monnet et al 1990). Similarly, in the same electrophysiological paradigm, 2-APHB, a structural analog of DTG but with no affinity for σ receptors, has no effect on the activation induced by NMDA at doses up to 1 mg/kg.

This potentiation of the effect of NMDA by some sigma ligands may appear surprising since benzomorphans and some sigma ligands, such as (+)SKF-10,047, have been reported to antagonize the NMDA response (Anis et al 1983; Lodge et al 1988; Malouf et al 1988a; Martin and Lodge 1988; Aram et al 1989). Two different interpretations could explain these discrepancies: as mentioned above, these inhibitory effects of the sigma ligands were obtained with much higher doses (three orders of magnitude) and could therefore be correlated with their affinity for the PCP site. However, recent data have also shown that low doses of DTG could also have an inhibitory effect on NMDA- induced activation in the CA_1 region or after a destruction of the pre-synaptic sigma receptors on mossy fibres projecting to the CA_3 region. Hence, the inhibitory effects of sigma ligands in the previous studies might also be ascribed to the involvement of different subtypes of sigma receptors (Debonnel et al 1992).

It has been reported that NMDA can evoke the release of [^{3}H]NE from pre-loaded hippocampal slices in a concentration-dependent manner (Jones et al 1987; Snell et al 1987; Fink et al 1989; Gothert and Fink 1989). To determine if this response to NMDA could also be modulated by sigma ligands, the effects of DTG, (+)3-PPP, JO-1784 and haloperidol on NMDA evoked [^{3}H]NE release from preloaded hippocampal slices were studied *in vitro*. In this model, JO-1784 and (+)3-PPP potentiate, whereas DTG inhibits, the NMDA-induced release of [^{3}H]NE. Haloperidol does not modify the NMDA-evoked [^{3}H]NE release, but completely prevents the effects of JO-1784 and DTG. In contrast, spiperone fails to reverse the effect of JO-1784 and (+)3-PPP (Monnet et al 1992a).

These results also suggest that sigma receptors are involved in the modulation of the effect of NMDA. However, the opposite profiles of action of DTG and (+)3-PPP in the *in vivo* and *in vitro* models constitute another argument suggesting that these effects might be mediated through different subtypes of sigma receptors.

Since our first report, the modulation of the NMDA response by sigma ligands has been confirmed by other groups. Martin et al (1992) have replicated the electrophysiological observations. Iyengar et al (1990a; 1990b) have shown that intra-cerebroventricular injections of μg doses of (+)pentazocine and (+)SKF 10,047 modulate the release of ACTH and the metabolism of dopamine in A9 and in A10 by interacting with NMDA receptors, since these effects are suppressed by NMDA antagonists. The same group also reported that the sigma ligands BMY-14802, rimcazole (Ferris et al 1986), ifenprodil (Contreras et al 1990a), (+)SKF-10047 and dextromethorphan (Fujii et al 1970) antagonize the increase in mice cerebellar cGMP induced by intra-cerebellar injections of harmaline and serine, by an effect on NMDA receptors (Rao et al 1990a; 1991; Iyengar et al 1991). Finally, it has also been shown that ifenprodil and BMY-14802 possess a neuroprotective activity, presumably through a modulation of the NMDA function (Legendre and Westbrook 1991; Pontecorvo et al 1991).

Beside this modulation of the NMDA response, several sets of data suggest that sigma receptors might also modulate the activity of the dopaminergic system. In electrophysiological paradigms, the effects of sigma ligands have been studied in various brain areas. In the substantia nigra, DTG, (+)pentazocine and (+)3-PPP reduce the firing activity of dopamine neurons (Clark et al 1985; Steinfels et al 1989; French and Ceci 1990). This effect of (+)3-PPP can be reversed by BMY 14802 (Steinfels and Tam 1989), but not by the selective sigma ligand HW 173 (Largent et al 1988; Engberg and Wikström 1991). It is noteworthy that these data were obtained with doses of these sigma ligands ten to 500 times higher than the doses of spiperone which induced changes in the firing activity of these neurons (Steinfels et al 1989). In the same area, the acute administration of BMY-14802, but not of rimcazole, prevents and reverses the inhibition of the firing of dopaminergic neurons induced by apomorphine (Piontek and Wang 1986). A similar effect was found in A10 (Wachtel and White 1988). BMY-14802 alone has been reported to increase the spontaneous firing activity of A9 dopaminergic neurons (Steinfels et al 1989; Steinfels and Tam 1989) or to have an effect neither on A9 nor on A10 (Wachtel and White 1988). The acute intravenous administration of (+)SKF 10,047 and (+)pentazocine induces an increase of the firing activity of most of the A9 and A10 dopaminergic neurons (French and Ceci 1990; Freeman and Zhang 1992). However, such an effect could be obtained only with doses greater than 2 mg/kg and no consistent effect could be observed with local microiontophoretic applications of (+)SKF 10,047 (Freeman and Bunney 1984); furthermore, a similar excitatory effect in A10 was obtained with lower doses of PCP (French and Ceci 1990). High doses of JO-1784 and DTG were reported to be inactive in A10 (Freeman and Zhang 1992), rimcazole being the only sigma ligand reported to induce a decrease in the number of spontaneously active dopaminergic neurons in A9 but not in A10 (Piontek and Wang 1986). Chronic treatment with rimcazole increases the number of spontaneously active dopaminergic neurons in A10 but not in A9, whereas a chronic treatment with BMY-14802 reduces the number of spontaneously active dopaminergic neurons in A10 but not in A9 (Piontek and Wang 1986; Wachtel and White 1988; Freeman and Zhang 1992). Finally, it was also reported recently that sigma

ligands modulate the release of dopamine in striatal slices (Gonzalez and Werling 1992).

Several other effects of sigma ligands have been described, some of them suggesting that sigma receptors are implicated in movement disorders. As already mentioned, high concentrations of sigma receptors have been found in areas involved in the control of movement. Local microiontophoretic applications of DTG decrease the firing activity of the red nucleus neurons (Matsumoto and Walker 1988) and of Purkinje cells in the cerebellar cortex (Kim and Bickford 1992), two regions enriched in sigma receptors. Haloperidol and SKF 10,047 have similar effects, whereas clozapine (which has no affinity for sigma receptors and does not induce extrapyramidal symptoms in patients with schizophrenia) has no effect on the firing rate of these neurons (Matsumoto and Walker 1988; Steinfels et al 1989; Iwamoto 1989).

In biochemical paradigms, DTG, (+)pentazocine and haloperidol have been shown to potently block the stimulation of inositol phosphate production by the cholinergic agonist carbachol (Bowen et al 1988; 1990b), whereas (+)3-PPP and rimcazole are nearly ineffective in this model. The relationship between this effect and sigma receptors has been challenged, since DTG and (+)pentazocine have also a relatively high affinity for muscarinic M_1 receptors, compared with those of (+)3-PPP and rimcazole (DeHaven-Hudkins and Hudkins 1991 ; Hudkins and DeHaven-Hudkins 1991). However, data showing that this effect is not present in cell cultures devoid of $sigma_1$ receptors suggest that at least part of this effect is indeed mediated by sigma receptors (Cutts and Bowen 1992). Haloperidol is effective in increasing NE-stimulated phosphoinositide metabolism, while DTG, (+)pentazocine, (+)3-PPP and rimcazole are virtually ineffective at concentrations up to 1 mM (Candura et al 1990). Finally, the fact that JO-1784 and (+)SKF-10,047 potentiate whereas, DTG inhibits KCI-induced acetylcholine release in hippocampal slices suggests that sigma receptors are involved in regulating the cholinergic activity (Junien et al 1991).

Low doses of sigma ligands produce few behavioral effects, with the exception of the contralateral circling produced by micro-injections of (+)pentazocine in the substantia nigra (Goldstein et al 1989). As mentioned above, there appears to be a correlation between most of the behavioral effects observed with high doses of sigma ligands and their affinity for PCP but not with that for sigma receptors (Brent 1991; Sanger and Joly 1991).

These data clearly show that the issue of the physiological roles of sigma receptors is still confused. Depending on the model used, the same sigma ligand can act in opposite directions, suggesting the existence of several subtypes of sigma binding sites, which are more or less involved in each of these different models. Hence, much work remains to be done to fully elucidate the exact roles of these different subtypes of sigma receptors in modulating the NMDA response, the activity of dopaminergic and cholinergic systems, to mention only a few.

Different subtypes of sigma binding sites

Since the distinct nature of sigma and PCP binding sites has been established (Quirion et al 1987), several biochemical and binding studies have suggested the existence of distinct subtypes of sigma receptors (Itzhak 1987; 1989; Bowen et al 1989; Klein and Musacchio 1989; Musacchio et al 1989; Itzhak et al 1990; McCann and Su 1990a; Weber and Keana 1990; Karbon et al 1991; Karbon and Enna 1991; Knight et al 1991a; Woodruff et al 1991; Zhou and Musacchio 1991). We are still far from a general agreement on the number and precise definitions of these subtypes, but at least a consensus was reached, at a recent meeting on sigma and PCP receptors, on the existence of at least two receptors, denoted $sigma_1$ and $sigma_2$ (Quirion et al 1992b). The (+) isomers of sigma ligands would be more potent on $sigma_1$ receptors, whereas (-) isomers would have a higher affinity for $sigma_2$ receptors. A phenytoin and GTP sensitivity would be present only for $sigma_1$ receptors, which would be also down-regulated following chronic treatment with haloperidol. (+)Pentazocine, (+)SKF 10,047 and JO-1784 would act primarily on $sigma_1$ receptors, whereas DTG and haloperidol would bind with a high affinity to both subtypes of sigma receptors. However, no selective ligands for the $sigma_2$ receptors have yet been identified (Quirion et al 1992a; 1992b).

Electrophysiological observations also support the hypothesis of the existence of several subtypes of sigma receptors. For instance, it was found that DTG (at doses in between 5 and 10 μg/kg, i.v.) induces an epileptoid response to NMDA, whereas none of the other sigma ligands tested exhibits such an effect (Debonnel et al 1990b; Monnet et al 1990). Moreover, opposite effects of DTG and JO-1784 were found in the CA_1 from those in the CA_3 region (Debonnel et al 1992), in keeping with the data obtained with the [^{3}H]NE release model (Monnet et al 1992a).

The very existence of sigma receptors has recently been questioned. The fact that (+)SKF 10,047 binds with a high affinity in the liver membrane in rats, and that, in the brains of rats or guinea pigs, sigma receptors are more concentrated in microsomes than in synaptosomes, suggested a non-synaptic localization (McCann and Su 1990b; Knight et al 1991b). The fact that proadifen, a potent inhibitor of several forms of cytochrome P-450, displaces with a high affinity the sigma ligands [^{3}H]DTG, [^{3}H]3-PPP, [^{3}H]SKF 10,047, led to the suggestion that, in fact, sigma ligands might bind to the metabolic enzyme cytochrome P-450 and not to specific receptors (Ross 1990; Klein et al 1991; LaBella 1991; Lehmann 1991). However, several lines of evidence ruled out this possibility. First, the fact that several studies have shown functional effects specific to sigma ligands *in vivo* or *in vitro* would be difficult to reconcile with a mere binding to cyto-

chrome P-450. It has also been reported that spironolactone, a diuretic steroid which causes a depletion of microsomal cytochrome P-450, does not change the levels of [^{3}H]DTG binding in adrenals and ovaries, whereas phenobarbital, an inducer of cytochrome P-450, does change [^{3}H]DTG binding in liver but not in the brain of rats (Fleissner et al 1991; Sonders and Weber 1991). Moreover, several cytochrome P-450 inhibitors do not potently displace [^{3}H]DTG and [^{3}H](+)pentazocine binding (Basile et al 1992). Finally, we have shown that cytochromes P-450 are not involved in the modulation of NMDA-induced response in the CA_3 region of the dorsal hippocampus (Monnet et al 1993). Thus, it is conceivable either that the ligands used to mark cytochrome P-450 have also some affinity for the sigma receptors or that this enzyme represents one of the binding sites for sigma ligands.

Endogenous ligands for sigma receptors

Endogenous ligands for sigma receptors have not yet been identified, but several attempts have been made during the past few years. Su et al (1986) have isolated several fragments that they termed "sigmaphin" which displace the binding of [^{3}H]SKF 10,047. However, these fragments demonstrate also a relatively high affinity for μ and δ receptors. Contreras et al (1987a) isolated two peptidic extracts from porcine brains, one with an affinity for both PCP and sigma binding sites, whereas the second fragment appears to inhibit selectively the binding of [^{3}H]SKF 10,047. It has also been shown that several steroids, and especially progesterone, competitively displace [^{3}H]SKF 10,047 and [^{3}H]haloperidol. It has been therefore proposed that some of these molecules might represent the endogenous ligands for sigma binding sites (Su et al 1988; Schwarz et al 1989; Su et al 1989). Chavkin's group has shown that the depolarization of hippocampal slices *in vitro* reduces [^{3}H]DTG and [^{3}H]3-PPP binding (Neumaier and Chavkin 1989; Connor and Chavkin 1991). They proposed that this could be the result of the release of an endogenous ligand of sigma receptors, since this effect is calcium dependant and tetrodotoxin-sensitive. The nature of this phenomenon is not yet known; however, some data suggest that it might be caused by the release of Zn^{2+} (Connor et al 1992).

Roman et al (1989) reported that neuropeptide Y (NPY) has a high affinity for the rat brain sigma binding sites, labelled with (+)[^{3}H]SKF. Neuropeptide Y (NPY) is a 36 amino acid peptide found in high concentration both in the peripheral and central nervous systems, being particularly abundant in limbic structures (Martel et al 1988; Danger et al 1990). NPY affects several physiological functions, including memory processing and motor activities (Dumont et al 1992).

In our electrophysiological model, similarly to the sigma agonists, NPY selectively potentiates the activation of CA_3 pyramidal neurons induced by NMDA (Monnet et al 1992b; Monnet et al 1992c). To date, three types of NPY receptors have been identified, denoted Y_1, Y_2 and Y_3. These subtypes of receptors are believed to mediate most of the physiological effects of NPY, and of several fragments of NPY or related peptides. To determine the subtype of receptor involved in this effect of NPY, several fragments or related peptides, known to act preferentially on one of these subtypes, were tested. The effect of NPY is mimicked by [Leu^{31}, Pro^{34}]NPY and NPY_{13-36} but not by all other fragments or related peptides tested, such as PP or PYY. The latter peptide and NPY_{18-36} act as antagonists. These data suggest that this effect is not mediated via the Y_1, Y_2 or Y_3 receptors, but via another subtype of NPY receptor (Monnet et al 1992c). Since the effects of NPY, [Leu^{31}, Pro^{34}]NPY and NPY_{13-36} are suppressed by haloperidol and BMY-14802, but not by spiperone, this NPY receptor might represent a subtype of a sigma receptor (Monnet et al 1992b). This contention is supported by the demonstration that *in vitro,* NPY, similarly to sigma ligands, potentiates the release of NMDA-evoked [^{3}H]NE release from hippocampal slices (Roman et al 1991), and also by the fact that NPY, similarly to the sigma ligand JO-1784, increases ion transport in the isolated jejunum of mice and rats, an effect which is reversed by haloperidol (Pascaud et al 1990; Riviere et al 1990).

Despite several attempts to replicate the *in vitro* observation of Roman et al (1989), the displacement by NPY of the binding of [^{3}H] sigma ligands could not be confirmed *in vitro* by other groups (Tam and Mitchell 1991; Bouchard et al 1992). However, the displacement of sigma ligands by NPY and NPY fragments was observed *in vivo* (Bouchard et al 1992; 1993). In conclusion, these data raise the possibility that NPY might be the endogenous ligand for at least one subtype of sigma receptor, but more studies are needed to confirm this hypothesis (Debonnel et al in press).

Sigma receptors and psychiatry

The involvement of sigma receptors in some psychiatric disorders was first suggested by the psychotomimetic effects of (+)SKF 10,047 and analogs. However, the exact role of sigma receptors in these effects remains controversial. Musacchio (1990), from a review of available clinical studies, concluded that the psychotomimetic effects were induced by the levorotary isomers, could be reversed by naloxone, and thus were likely to be attributable to the activation of classical κ opiate receptor. More recently, Su (1991) reviewed the same data and challenged these conclusions, maintaining that the psychotomimetic effects of these drugs are mediated by the activation of sigma receptors.

Beside the induction of psychotomimetic effects by sigma ligands, the potential implication of sigma receptors in the pathophysiology or in the treatment of schizophrenia is also suggested by the affinity of several classical neuroleptics for these receptors and by the claim that new molecules (such as BMY-14802, remoxipride, rimcazole, HW 173, umespirone,

Dup 734 and XJ 448) with a high affinity for sigma receptors and a low affinity for dopaminergic receptors, could be effective antipsychotic drugs (Ferris et al 1986; Su 1986; Taylor and Dekleva 1987; 1988; Largent et al 1988; Snyder and Largent 1989; Itzhak et al 1990; Asztely et al 1991; Cook et al 1992; Krause et al 1992). Some molecules, such as rimcazole and remoxipride, have been shown to exert an antipsychotic effect in open or double-blind studies in patients with schizophrenia (Munetz et al 1989; Den Boer et al 1990; King et al 1992). However, most of these molecules are still in phase I or at preclinical levels. Several other studies will be needed before reaching a definite conclusion regarding the potential usefulness of sigma ligands as antipsychotic agents.

Another argument in favor of the implication of sigma receptors in schizophrenia are the reports of post-mortem studies from several groups showing a reduction of sigma binding sites in several cortical regions and in the cerebellum of patients with schizophrenia. This reduction is apparently due to a reduction in the number of binding sites with no change in affinity (Simpson et al 1990; Weissman et al 1991; Shibuya et al 1992). However, the fact that these patients had been treated for unknown periods of time with neuroleptics raises questions about the clinical significance of these findings, since chronic treatment with haloperidol induces a down-regulation of sigma binding sites in animals and humans (Itzhak and Alerhand 1989; Matsumoto et al 1990; Karbon and Enna 1991; Kizu et al 1991; Reynolds et al 1991). A clear answer to this other controversial aspect will be provided by post-mortem studies on the brains of patients with schizophrenia, not treated with neuroleptics or treated with neuroleptics without affinity for sigma receptors.

A last argument in favor of the implication of sigma receptors in psychiatry is the fact that cocaine, which is known to induce acute psychotic episodes and long-lasting delusional states, has a high affinity for sigma receptors (Sharkey et al 1988). The stimulant effects of cocaine are abolished by sigma antagonists such as haloperidol, BMY-14802 and (+)3-PPP (Menkel et al 1991), whereas chronic treatment with cocaine induces a supersensitivity of sigma receptors (Ujike et al 1992).

The precise mechanisms whereby sigma receptors may be implicated in schizophrenia needs to be established. However, several hypotheses can be envisaged.

The dopaminergic hypothesis of schizophrenia is based principally on a correlation between the affinity of neuroleptics for post-synaptic dopaminergic receptors and their antipsychotic potency. However, it has long been suggested that the hypothesis of a hyperactivity of the dopaminergic system could not entirely account for the pathogenesis of schizophrenia. This suggestion was pushed one step ahead by Hoffman (1990) who proposed that, contrary to what was originally supposed, the correlation between the D_2 binding affinity of neuroleptics and their clinical efficacy could in fact correspond to a correlation with sigma binding sites since these studies where done with [^{3}H]haloperidol as the marker for dopaminergic receptors. This conclusion is certainly somewhat premature. Nonetheless other hypotheses might be envisaged.

Several lines of evidence suggest that, beside dopamine, the glutamatergic system may play an important role in schizophrenia in different ways. A dysfunction of glutamatergic neurons in cerebral areas, particularly in the frontal and left temporal cortices, and in the hippocampus (Deakin et al 1989; Jeste and Lohr 1989) has been suggested to be directly involved in the pathophysiology of schizophrenia (Kim et al 1980). It has also been postulated that glutamatergic pathways are involved in the pathophysiology of the negative symptoms of schizophrenia (Kornhuber and Fischer 1982). An indirect effect of GLU is also possible since the glutamatergic and the dopaminergic systems are reciprocally modulating each other. The glutamatergic cortico-striatal pathways modulate the dopamine release in subcortical structures, such as the nucleus accumbens and the striatum, whereas glutamatergic receptors are present on terminals of nigro-striatal dopaminergic neurons (Schwarz et al 1978; Crawford and Roberts 1989). The purported hyperactivity of the dopaminergic system in schizophrenia could therefore result from or induce the glutamatergic deficiency found in this pathology (Kim et al 1980; Deutsch et al 1989; Carlsson and Carlsson 1990; Wachtel and Turski 1990; Sherman et al 1991a; 1991b; Taylor et al 1992). At any rate, in both cases, sigma receptors, by modulating the neuronal response to the activation of NMDA receptors by glutamate, may play a pivotal role.

The involvement of sigma receptors via a direct interaction with dopaminergic neurons has also been proposed. As mentioned above, autoradiographic studies have demonstrated the presence, in the substantia nigra, of sigma receptors which are particularly abundant in a subdivision of this area enriched in D_2 dopaminergic receptors (Graybiel et al 1989), suggesting the possibility of a modulation of dopaminergic neurons by sigma receptors (Parker and Cubeddu 1985). The reduction of the sigma binding following the selective destruction of these neurons further indicates that sigma receptors could be localized on dopaminergic neurons (Gundlach et al 1986). Hence, these data together suggest the existence of pre- and post-synaptic sigma receptors in this area and could explain the diversity of the data obtained in the electrophysiological studies.

Finally, the possibility that sigma receptors might also be involved in other psychiatric disorders remains open since several antidepressants, such as sertraline, opipramol, deprenyl and clorgylline, also have very high affinity for sigma receptors (Musacchio et al 1987; Klein and Musacchio 1989; Schmidt et al 1989; Itzhak and Kassim 1990; Itzhak and Stein 1990; Rao et al 1990b; 1990c); some of them have been shown to exert the same modulatory effect on the NMDA response as classical sigma ligands (Bergeron et al 1992).

In conclusion, all the data obtained thus far seem to indicate that several subtypes of sigma receptors exist in the central nervous system. By modulating the neuronal responses mediated via the glutamatergic pathways, by regulating directly the firing activity of dopaminergic neurons, or by both mechanisms, sigma ligands could play a major role in the pathophysiology of schizophrenia. Further studies aimed at a better understanding of their specific effects might open innovative avenues in the treatment of this pathology.

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