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European Journal of Pharmacology 401 (2000) 155–160

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Correlation between neuroleptic binding to σ_1 and σ_2 receptors and acute dystonic reactions

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Received 20 March 2000; received in revised form 15 June 2000; accepted 20 June 2000

Abstract

Acute dystonic reactions are motor side effects that occur soon after the initiation of neuroleptic treatment. Although earlier studies indicate that these abnormal movements can be induced in animals and humans via activation of σ receptors, the relative contribution of the different σ receptor subtypes is unknown. Since σ_1 and σ_2 receptor are differentially represented in motor regions of the brain, the affinities of 17 neuroleptics for these σ receptor subtypes were determined using competition binding studies. The results revealed that most neuroleptics do not exhibit selectivity for either of the σ receptor subtypes, as reflected by a significant correlation between the affinities of the neuroleptics for σ_1 vs. σ_2 receptors. Moreover, when the σ binding affinities of the neuroleptics were correlated with the tendency of the drugs to produce acute dystonic reactions in humans, there was a significant correlation for both subtypes. Together with earlier studies in animals, the data suggest that neuroleptic-induced motor side effects can be mediated through both σ_1 and σ_2 receptors.

Keywords: σ Receptor; Neuroleptic; Haloperidol; Dystonia; Extrapyramidal

1. Introduction

Many typical antipsychotic drugs interact with σ receptors, in addition to producing actions through dopamine receptors (Tam and Cook, 1984). σ Receptors can be distinguished from dopamine receptors by their unique distribution in the brain, profile of compounds that interact with them, and amino acid sequence (Hanner et al., 1996; Pan et al., 1998; Seth et al., 1997; cf. Walker et al., 1990). The nature and structure of σ receptors are still being elucidated, with information about their functional relevance being derived largely from pharmacological studies.

The ability of neuroleptics to interact with σ receptors led to initial speculations that these proteins are involved in the antipsychotic properties of the drugs. However, unlike the correlation between the affinities of neuroleptics for dopamine D_2 receptors and their therapeutic doses in humans, a comparable relationship does *not* exist for σ receptors (Walker et al., 1990). Several lines of evidence suggest that instead, σ receptors mediate the motor side effects of antipsychotic drugs.

The anatomical evidence supporting a role for σ receptors in the motor side effects of neuroleptics is compelling. The muscles most often afflicted in neuroleptic-induced motor side effects are controlled by brainstem nuclei that are especially rich in σ receptors (Bouchard and Quirion, 1997; McLean and Weber, 1988). The cranial nerve nuclei that subserve eye movements (oculomotor, abducens, trochlear) are densely concentrated with σ receptors, as are the hypoglossal, facial, and motor trigeminal which comprise the final common pathways for lingual, facial, and masticatory movements. The tendency of neuroleptics to affect buccal, oral, lingual and facial movements (as in tardive dyskinesia) and eye movements (as in oculogyric crises) coincides with the anatomical distribution of σ receptors. In the basal ganglia, significant levels of σ receptors are found in the substantia nigra, particularly the dopaminergic pars compacta (Gundlach et al., 1986). Furthermore, the cerebellum and red nucleus, motor nuclei with historic ties to dystonia (Stanley et al., 1983; Zweig

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0014-2999/00/$ - see front matter
PII: S0014-2999(00)00430-1

and Hedreen, 1988) contain high concentrations of σ receptors (Bouchard and Quirion, 1997; Gundlach et al., 1986; McLean and Weber, 1988).

Earlier studies demonstrate that acute dystonic reactions can be elicited by σ-active neuroleptics such as haloperidol and selective σ receptor agonists when microinjected into the rat red nucleus (Matsumoto et al., 1990; Walker et al., 1988). This effect appears mediated through σ receptors because there is a significant correlation between the ability of compounds to produce acute dystonic reactions in animals and their σ binding affinities (Matsumoto et al., 1990). In contrast, microinjections of ligands that target dopamine (sulpiride, SCH 23390 [*R*-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine]), opiate (morphine, naloxone), NMDA (phencyclidine), 5-HT (serotonin, 8-OH-DPAT [(±)-8-hydroxy-2-dipropylaminotetralin]), acetylcholine (scopolamine, oxotremorine), or norepinephrine (isopropanolol, propranolol) receptors fail to elicit these abnormal postures after comparable administration (Matsumoto and Walker, 1991; Matsumoto et al., 1990, 1995; Walker et al., 1988). Aside from acute dystonic reactions, orofacial dyskinesias can also be produced after microinjection of haloperidol or the selective σ ligand di-*o*-tolylguanidine (DTG) into the facial nucleus of rats (Tran et al., 1998). Furthermore, the ability of novel σ receptor antagonists to attenuate acute dystonic reactions and orofacial dyskinesias in animals demonstrates not only a receptor-mediated mechanism, but also a potential therapeutic strategy for preventing these unwanted movements (Matsumoto et al., 1995; Tran et al., 1998).

In contrast to the dystonia and dyskinesia elicited by σ receptor agonists, atypical neuroleptics such as clozapine and sulpiride, which do not interact with σ receptors (cf. Walker et al., 1990), also fail to produce dystonia and dyskinesia after intracerebral microinjection in rats (Matsumoto et al., 1990; Tran et al., 1998; Walker et al., 1988). Since clozapine and sulpiride are associated with a low risk for producing motor side effects in humans (Collaborative Working Group on Clinical Trials Evaluations, 1998), an association between neuroleptic binding to σ receptors and their ability to induce motor side effects is suggested.

To test this, the σ binding affinities of 17 neuroleptics that vary in their tendency to produce acute dystonic reactions were determined. Of the two most established σ receptor subtypes, the σ_2 receptor is thought to have an important role in motor function (Walker et al., 1993). In contrast, σ_1 receptors are thought to have a lesser role in motor function (Matsumoto et al., 1995; McCracken et al., 1999a), although their implications for neuroleptic-induced motor side effects are still unclear. Therefore, the σ_1 and σ_2 affinity for each neuroleptic was correlated with the incidence of the drug for producing acute dystonic reactions in humans. This latter measure was determined from a retrospective literature review.

2. Materials and methods

The radioligands were obtained from NEN Life Sciences (Boston, MA). (+)-Pentazocine was supplied by the NIDA Chemical Synthesis Program (Bethesda, MD). All other chemicals and drugs were purchased from commercial suppliers (Aldrich, Milwaukee, WI; Research Biochemicals, Natick, MA; Sigma, St. Louis, MO).

Since σ receptors appear well conserved across species (Barnes et al., 1992; Vu et al., 1990), the affinities of neuroleptics for these receptors were determined in rat brain using radioligand binding assays. Furthermore, whole brain was used rather than tissue from only motor nuclei because there is no evidence that the amino acid sequence or structure of a given σ receptor subtype varies in different regions of the brain. In addition, since under clinical conditions, the neuroleptics affect all brain regions, not only motor areas, tissue from the entire brain was relevant. The methods for the receptor binding assays were

Table 1
Affinities of neuroleptics for σ receptors

Ligand	σ_1	σ_2	$\sigma_1 + \sigma_2$
Neuroleptics			
Haloperidol	3±0.3	54±10	11±1
Trifluperidol	12±1	121±30	19±2
Reduced haloperidol	22±4	46±6	31±2
BMY 14802	66±11	51±8	36±5
Remoxipride	71±3	319±52	121±4
Fluphenazine	109±29	208±62	164±43
Metoclopramide	180±46	>10,000	250±26
Trifluoperazine	265±11	574±99	223±36
Haloperidol metabolite I	362±20	>10,000	520±190
Chlorpromazine	453±95	1628±159	794±132
Cis-(*z*)-flupenthixol	597±67	268±10	160±11
Trifluopromazine	1135±141	1875±592	765±78
Thioridazine	1362±656	1239±183	602±70
Risperidone	1392±339	1713±661	1091±134
Pimozide	1555±284	3274±278	1409±409
Rimcazole	2380±812	1162±160	1314±429
S(−)-raclopride	5123±1195	>10,000	2456±228
Sulpiride	>10,000	>10,000	>10,000
Clozapine	>10,000	>10,000	>10,000
Haloperidol metabolite III	>10,000	>10,000	>10,000
Reference compounds			
DTG	77±5	43±9	49±4
SCH 12679	>10,000	>10,000	>10,000
Scatchard analysis			
K_d (nM)	10±1	53±3	48±1
B_{max} (fmol/mg)	289±21	1020±97	1427±21

The affinities (K_i in nM) were determined in rat brain homogenates. [^{3}H](+)-Pentazocine was used to label σ_1 receptors. [^{3}H]DTG + 300 nM (+)-pentazocine (to mask σ_1 sites) was used to label σ_2 receptors. [^{3}H]DTG binding (combination of σ_1 and σ_2 receptors) is indicated in the last column. Non-specific binding was determined in the presence of haloperidol. Affinities of >10,000 nM signify that there was less than 30% displacement of the radioligand at that concentration.

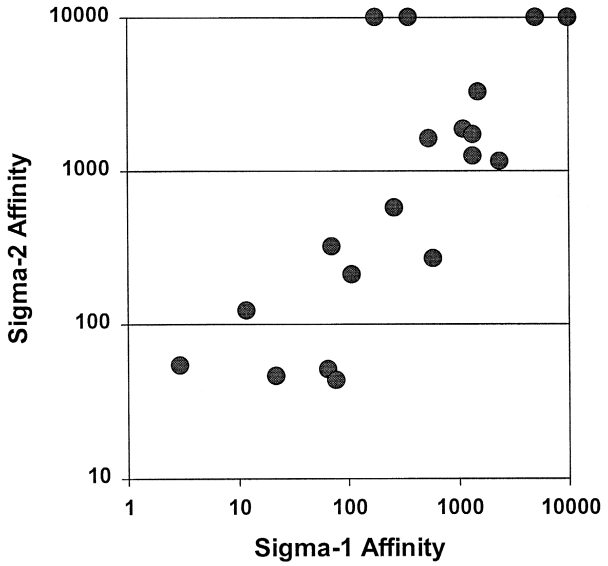

Fig. 1. Relationship between affinities of neuroleptics for σ_1 and σ_2 receptors. There was a significant correlation between the affinities of neuroleptics for σ_1 and σ_2 receptors ($P < 0.001$).

performed as described previously (Bowen et al., 1993; Matsumoto et al., 1995), with minor modifications. Briefly, crude P_2 membranes were prepared from the brain minus cerebellum of male, Sprague–Dawley rats (150–200 g; Harlan, Indianapolis, IN). σ_1 Receptors were labeled with 5 nM [^{3}H](+)-pentazocine (28 Ci/mmol). σ_2 Receptors were labeled with 3 nM [^{3}H]di-*o*-tolylguanidine (31 Ci/mmol) in the presence of 300 nM (+)-pentazocine (to mask σ_1 sites). $\sigma_1 + \sigma_2$ Receptors were labeled with 3 nM [^{3}H]di-*o*-tolylguanidine. Non-specific binding was determined in the presence of 10 -μM haloperidol. Competition binding studies were performed using 13 concentrations of each test compound. Data from the binding studies were analyzed using GraphPad Prism (San Diego, CA). Pearson product moment correlation coefficient was used to determine whether there was a significant correlation between the affinities of the neuroleptics for σ_1 vs. σ_2 receptors.

In addition, the affinities of neuroleptics for σ receptors as determined in the receptor binding assays were correlated with their risk for producing acute dystonic reactions in humans using Spearman rank–order correlations. The risk for producing acute dystonic reactions in humans was determined using a retrospective literature-based method modified from Jeanjean et al. (1997): 1 = lower than 1%, 2 = between 1% and 5%, 3 = between 5% and 15%, 4 = between 15% and 30%, 5 = higher than 30%. The following neuroleptics were assigned ranks based on the references cited: haloperidol (Addonizio and Alexopoulos, 1988 [20%]; The British Isles Raclopride Study Group, 1992 [21%]; Goff et al., 1991 [33%]; Itoh, 1985 [11%]; Magliozzi et al., 1985 [33%]; Remington et al., 1990 [65%]; Silverstone et al., 1984 [33%]; Sramek et al., 1986 [38%]; Swett, 1975 [16%]), fluphenazine (Addonizio and Alexopoulos, 1988 [25%]; Ayd, 1961 [12%]; Chakos et al., 1992 [36%]; Chouinard et al., 1970 [10%]; Simpson, 1970 [12–30%]; Sramek et al., 1986 [18%]; Swett, 1975 [12%]), metoclopramide (Edge et al., 1987 [32%]; Hainsworth et al., 1991 [5%]; Howrie et al., 1986 [45%]; Sorbe and Hallen, 1998 [3%]), trifluoperazine (Ayd, 1961 [8%]; Edwards et al.,

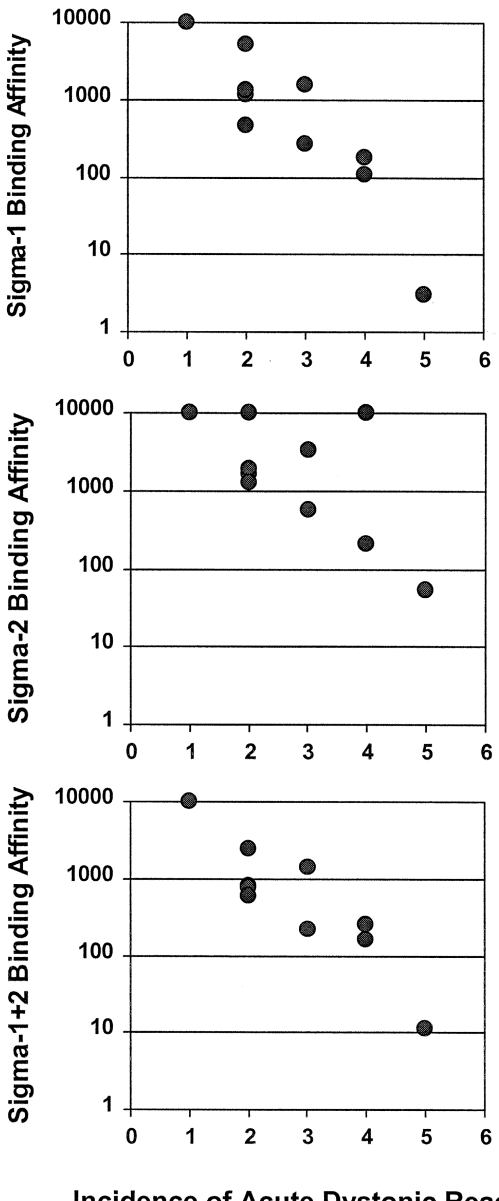

Fig. 2. Relationship between acute dystonic reactions in humans and σ binding affinities of neuroleptics. The affinities of neuroleptics for σ receptors were determined in rat brain homogenates. The rank order for the incidence of dystonia was determined from a retrospective literature review, with higher ranks associated with a higher incidence of dystonia. There was a significant correlation with binding to σ_1 receptors that were labeled with [^{3}H](+)-pentazocine ($P < 0.01$), with binding to σ_2 receptors that were labeled with [^{3}H]DTG in the presence of a saturating concentration of (+)-pentazocine ($P < 0.05$), and with binding to $\sigma_1 + \sigma_2$ receptors that were labeled with [^{3}H]DTG ($P < 0.01$).

1980 [10%]; Swett, 1975 [8%]), chlorpromazine (Ayd, 1961 [1%]; Harnryd et al., 1984 [0%]; Relling et al., 1993 [3%]; Sramek et al., 1986 [0%]; Swett, 1975 [4%]), trifluopromazine (Ayd, 1961 [3%]), thoridazine (Greenhill et al., 1985 [6%]; Keks et al., 1994 [2%]; Swett, 1975 [0.6%]), pimozide (Chouinard et al., 1970 [0%]; cf. Opler and Feinberg, 1991 [0%]; Silverstone et al., 1984 [30%]), raclopride (The British Isles Raclopride Study Group, 1992 [2%]), sulpiride (Edwards et al., 1980 [0%]; Gerlach et al., 1985 [0%]; Harnryd et al., 1984 [0%]; Mielke et al., 1977 [0%]), clozapine (Daniel et al., 1996 [0%]; Kurz et al., 1995 [0%]). For each drug, the percent of acute dystonic reaction cited in each paper was averaged then converted to a rank.

3. Results

The affinities of the neuroleptics for σ_1 and σ_2 receptors are summarized in Table 1. There was a significant correlation between the affinities of neuroleptics for σ_1 vs. σ_2 receptors ($r = 0.72$, $P < 0.001$; Fig. 1). The relationship between neuroleptic binding to the various σ receptor subtypes and their incidence of producing acute dystonic reactions in humans is summarized in Fig. 2. There was a significant correlation between the tendency of neuroleptics to elicit acute dystonic reactions in humans and their affinities for σ_1 receptors ($r = 0.92$, $P < 0.01$). The correlation with binding to σ_2 receptors was barely significant when metoclopramide, which is inactive at σ_2 receptors, was included in the analysis ($r = 0.69$, $P < 0.05$). When metoclopramide was excluded, the relationship to σ_2 binding became very significant ($r = 0.91$, $P < 0.01$). There was also a significant correlation between the incidence of dystonia and σ binding, when the binding assay did not discriminate between the subtypes ($r = 0.91$, $P < 0.01$).

4. Discussion

There was a significant relationship between the ability of neuroleptics to interact with σ receptors and their tendency to elicit acute dystonic reactions in humans. Most neuroleptics do not have a preference for σ_1 vs. σ_2 receptors, and there is a significant correlation between the affinities of neuroleptics for the two subtypes.

One drug that was an exception in terms of subtype selectivity was metoclopramide. Metoclopramide has moderate affinity for σ_1 receptors, but appears inactive at σ_2 receptors. Metoclopramide is also associated with a high risk for producing acute dystonic reactions in humans, suggesting the importance of the σ_1 subtype in this effect. Together with the highly significant correlation between the ability of a wide range of neuroleptics to interact with σ_1 receptors and their tendency to produce acute dystonic reactions in humans, the data suggest that σ_1 receptors are involved in the motor side effects of neuroleptics.

In addition to metoclopramide, haloperidol metabolite I, the chlorophenyl-hydroxy-piperidine metabolite of haloperidol, also had significant affinity for σ_1 receptors, but was inactive at σ_2 receptors. It has previously been suggested that the combined accumulation of haloperidol and its metabolites contributes to the high incidence of motor side effects normally associated with this neuroleptic (Bowen et al., 1990). Since these metabolites retain significant affinities for σ receptors, but lose their affinities for dopamine D_2 receptors, as compared to haloperidol, the importance of σ-mediated actions over time has been proposed (Bowen et al., 1990). In this regard, it is noteworthy that the σ-active metabolites of haloperidol all have significant affinities for σ_1 receptors, indicating the potential importance of this subtype in the actions of haloperidol, particularly as metabolism proceeds.

In addition to σ_1 receptors, the contribution of σ_2 receptors in acute dystonic reactions is likely. In the present study, there was a significant correlation between σ_2 binding and acute dystonic reactions in humans. The apparent importance of this subtype is further supported by earlier studies demonstrating the involvement of σ_2 receptors in motor function (Walker et al., 1993). In addition, a previous study reported a correlation between acute dystonic reactions in humans and σ_2 binding in rat cerebral cortical membranes (Jeanjean et al., 1997). Unfortunately, the binding assays in this earlier study were performed with [^{3}H](+)-3PPP as the radioligand (Jeanjean et al., 1997), and (+)-3PPP has been shown to have high affinity for both σ_1 and σ_2 receptors (Bowen et al., 1993). Although not discriminating between the subtypes, this earlier study did describe a strong relationship between the incidence of acute dystonic reactions in humans and neuroleptic binding to σ receptors, as opposed to dopamine (D_2) and muscarinic receptors (Jeanjean et al., 1997). The present study thus represents an effort to clarify the relative contribution of the two σ receptor subtypes.

Although earlier studies have tended to emphasize the importance of the σ_2 subtype in motor function (Bouchard and Quirion, 1997; Matsumoto et al., 1995; McCracken et al., 1999a,b; Walker et al., 1993, 1994), the involvement of σ_1 receptors should not be discounted. In addition to the present data, numerous lines of evidence demonstrate the ability of σ_1 receptors to alter motor function. Autoradiographic studies show that σ_1 and σ_2 receptors co-exist in motor regions of the brain (Bouchard and Quirion, 1997). In the red nucleus, a brain region that mediates σ-induced acute dystonic reactions in animals, σ_1 receptors are found in relative abundance as compared to the σ_2 subtype. In addition, selective σ_1 receptor agonists have motor activating effects (Goldstein et al., 1989; Gudelsky, 1995; Patrick et al., 1993), while antisense oligodeoxynucleotides that inhibit the synthesis of σ_1 receptors attenuate motor behavior (Matsumoto and McCracken, 1999).

Together, the data support the significance of σ_1 receptors in motor function, along with the already established role of σ_2 receptors.

In addition to broadening our understanding of motor function in general, an involvement of σ receptors in neuroleptic-induced acute dystonic reactions can explain several risk factors in humans. Younger individuals are at higher risk for neuroleptic-induced acute dystonic reactions (Keepers and Casey, 1991), which is consistent with changes in σ receptor levels across age, where the receptor levels are highest in young adulthood (Hemstreet et al., 1993). These age-related differences in receptor levels are correlated with age-related differences in the ability of a selective σ receptor agonist to elicit acute dystonic reactions in animals (Hemstreet et al., 1993; Matsumoto et al., 1989). Furthermore, young adult males are particularly at risk for neuroleptic-induced acute dystonic reactions. This is a group in which the σ-active steroid testosterone is present in high levels (Su et al., 1988). Given that another risk factor is illicit drug use (Hegarty et al., 1991; Van Harten et al., 1998), it is noteworthy that many drugs of abuse, including cocaine, have significant affinities for σ receptors (Sharkley et al., 1988). Recent studies further show that these drugs elicit motor stimulant actions that can be attenuated with selective σ receptor antagonists or antisense oligodeoxynucleotides (Matsumoto and McCracken, 1999; McCracken et al., 1999a,b). Thus, many of the groups at risk for neuroleptic-induced acute dystonic reactions have higher levels of σ receptors and/or increased exposure to endogenous or exogenous σ receptor agonists.

Together, the data suggest that σ receptors have important implications for the risk of neuroleptic-induced motor side effects. Contrary to earlier reports that have indicated a predominant role for σ_2 receptors in motor function, the data also suggest the importance of σ_1 receptors.

Acknowledgements

This work was supported by a grant from the U.S. P.H.S. (MH50564).

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