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Extended Radioligand Binding Profile of Iloperidone: A Broad Spectrum Dopamine/Serotonin/Norepinephrine Receptor Antagonist for the Management of Psychotic Disorders

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Iloperidone is a novel psychotropic compound currently undergoing Phase III trials. Its affinity for human dopamine and 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors has been reported previously (Kongsamut et al. 1996). This report presents the affinity of iloperidone for a largely extended number of human neurotransmitter receptors. In a few instances human receptors were not available and receptor studies were performed on tissues from laboratory animals. The present data, supplemented with those of Kongsamut et al. (1996), indicate that iloperidone displays high affinity ($K_I <$ 10 nM) for norepinephrine α_1-adrenoceptors, dopamine D_3 and serotonin 5-HT$_{2A}$ receptors. Intermediate affinity (10–100 nM) was found for norepinephrine α_{2C}-adrenoceptors, dopamine D_{2A} and D_4 receptors and serotonin 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{2C}$ and 5-HT$_6$ receptors. The affinity for all other receptors was below 100 nM, including norepinephrine α_{2A}, α_{2B}, β_1, and β_2, muscarine M_1–M_5, histamine H_1, dopamine D_1 and D_5, CCK$_A$ and CCK$_B$, 5-HT$_7$, dopamine and norepinephrine transporters. Thus, iloperidone targets a selective set of dopamine, norepinephrine and serotonin receptor subtypes. The affinity for this particular set of receptors indicates that iloperidone has the potential to be a broad spectrum antipsychotic, with efficacy against positive, negative, depressive and cognitive symptoms of schizophrenia, and a low propensity to induce side effects.
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KEY WORDS: *Receptor binding profile; Psychotic disorders; Iloperidone; Adrenergic receptors; Dopamine receptors; Serotonin receptors*

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The prototypical classical neuroleptic agent haloperidol is an effective antipsychotic compound (Leucht et al. 1999) which, unfortunately, also induces severe extrapyramidal side effects (EPS) and hyperprolactinemia. The term "atypical antipsychotic" was originally introduced to describe compounds, such as clozapine, which not only suppressed psychotic symptoms, but differed from haloperidol by having a low tendency to induce EPS and increase plasma prolactin levels. It is postulated that dopamine D_2 receptor blockade is the mechanism by which antipsychotic activity is achieved (Creese et al. 1976; Seeman et al. 1976). However, since

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clozapine also interacts with D_2 receptors it is likely that there are additional properties embedded in the clozapine molecule that explain its "atypicality." One influential theory was put forward by Meltzer et al. (1989), who suggested that about a 10-fold higher affinity for serotonin 5-HT_{2A} over D_2 receptors could be the key factor in achieving improved clinical response and absence of EPS. This hypothesis has led to the development of new antipsychotics with the desired 5-HT_{2A}/D_2 affinity ratio, although each of these compounds also binds to additional receptor sites. Several of these novel antipsychotic compounds indeed display clear benefits in terms of side-effect profile. Interestingly, clozapine is active in schizophrenic patients who are treatment-refractory to other antipsychotics, including the more recent 5-HT_{2A}/D_2 receptor antagonists (Wahlbeck et al. 1999; Conley et al. 1999; Taylor and Duncan-McConnell 2000). The elucidation of the multiple receptor interactions of clozapine suggested that other neurotransmitter systems may also play a role in the efficacy and tolerability of that molecule. Particularly, the antiadrenergic effects of clozapine are now receiving increased attention (Nutt 1994; Litman et al. 1996; Hertel et al. 1999). Iloperidone is a new psychotropic agent currently undergoing Phase III trials for the treatment of psychotic disorders (Figure 1). Iloperidone was selected from a large series of piperidinyl-benzisoxazoles because it showed a 300-fold greater potency in a test for limbic activity (inhibition of apomorphine-induced climbing) than in a test for nigrostriatal activity (inhibition of apomorphine-induced stereotypy) (Strupczewski et al. 1995). The large difference of potency of iloperidone in these tests is expected to result in an improved ratio of therapeutic effect to EPS liability compared with standard antipsychotics.

Previous studies have investigated the receptor binding profile of iloperidone with rat receptors (Szewczak et al. 1995) and a limited number of human homologues of dopamine and 5-HT receptor subtypes (Kongsamut et al. 1996). These experiments demonstated that iloperidone displays the desired 5-HT_{2A}/D_2 affinity ratio. The aim of the present study was to determine the receptor affinity profile of iloperidone at a wider range of human neurotransmitter receptors. In resemblance to clozapine, it was noted that iloperidone possesses high affinity for norepinephrine α_1- and α_{2C} adrenergic receptors.

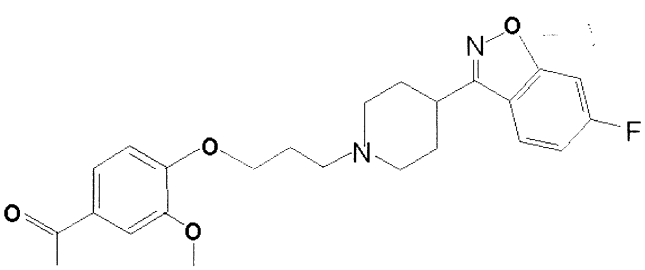

Figure 1. Chemical structure of iloperidone.

METHODS

The radioligand receptor binding assays are listed in Table 1.

Materials

Radioligands were purchased from NEN Life Science Products, USA, except for ^{3}H-RX821002 and ^{3}H-Mesulergine, which were obtained from Amersham Pharmacia Biotech Ltd, UK, and ^{125}I-GTI which was obtained from ANAWA, Switzerland. Iloperidone was synthesized by Hoechst Marion Roussel. Unless specified otherwise, all other chemicals were of reagent grade and obtained through standard commercial sources.

Membrane Preparation

Total rat brain (minus cerebellum) membranes were purchased from Analytical Biological Services (ABS) and prepared according to the following customer-supplied protocol. Male Wistar albino rats (250–300 g) were decapitated, the brains removed, the cerebral cortices dissected out and the rest of the brains homogenized in 10 volumes of ice-cold 50 mM Tris-HCl buffer, pH 7.7, for 30 s. The homogenate was centrifuged at 1000 g for 10 minutes, the supernatant collected and centrifuged at 35,000 g for 10 minutes. The pellet was resuspended in buffer and washed by four further 10-min centrifugations at 35,000 g. The final pellet was resuspended in buffer (2 mL/brain) and aliquots (2 mL) were frozen and stored at -80°C. Prior to use, the membrane suspension was thawed quickly at 37°C, centrifuged at 35,000 g for 10 minutes, washed once by suspension in the assay buffer and recentrifuged. The final pellet was resuspended and homogenized in the assay buffer to give the desired membrane concentration.

Guinea pig brain (minus cerebellum) membranes were also purchased from ABS and prepared according to the above protocol for rat brain membranes. The guinea pigs used were male Dunkin-Hartley with a 250–300 g body weight.

Calf brains were obtained from the local slaughterhouse and the caudate dissected over ice. Membranes were prepared as described previously (Bruinvels et al. 1992).

Cell membranes from Chinese hamster ovary (CHO) cell lines expressing recombinant α_{2A}, α_{2B}, α_{2C}, and $CRF_{2\alpha}$, and cell membranes from human embryonal kidney (HEK) 293 expressing recombinant D_{2A} and 5-HT_3, were prepared in the Nervous System Department, Novartis Pharma, Basel, Switzerland. They were

Table 1. Affinity Profile of Iloperidone for Human Receptors

Receptor	Radioligand	Cell	Internal reference, K_I (nM)[a]	Iloperidone K_I (nM)
Adenosine A_1	^{3}H-DPCPX	CHO	CPA, 5.37	>10,000
Adenosine A_{2A}	^{3}H-NECA	CHO	NECA, 93.3	>10,000
Adenosine A_3	^{125}I-AB-MECA	CHO	NECA, 100	>10,000
α_{2A} adrenoceptor	^{3}H-RX821002	CHO	RX821002, 0.776	162
α_{2B} adrenoceptor	^{3}H-RX821002	CHO	RX821002, 3.47	162
α_{2C} adrenoceptor	^{3}H-RX821002	CHO	RX821002, 3.09	16.2
β_1 adrenoceptor	^{3}H-CGP12177	Sf9	Propanolol, 9.77	>10,000
β_2 adrenoceptor	^{3}H-CGP12177	Sf9	ICI118551, 3.55	>10,000
Cannabinoid$_1$	^{3}H-CP55940	HEK 293	WIN55212-2, 708	>10,000
Cholecystokinin$_A$	^{3}H-L-354,718	NIH 3T3	CCK 8-sulphated, 6030	>10,000
Cholecystokinin$_B$	^{3}H-L-365,260	NIH 3T3	CCK 8, 17.8	9333
$CRF_{2\alpha}$	^{125}I-Sauvagine	CHO	D-Phe CRF, 33.5	>10,000
Dopamine D_{2A}	^{3}H-Spiperone	HEK 293	(+)Butaclamol, 8.13	21.4
Dopamine transporter	^{3}H-WIN35428	CHO-K1	WIN35428, 25.7	2951
5-HT_{1A}	^{3}H-8-OH DPAT	CHO-K1	8-OH DPAT, 0.692	93.1
5-HT_3	^{3}H-GR65630	HEK293	5-HT, 871	>10,000
5-HT_6	^{3}H-LSD	HeLa	Methiothepin, 0.631	63.1
5-HT_7	^{3}H-Mesulergine	Sf9		112
Norepinephrine transporter	^{3}H-Nisoxetine	MDCK	GBR 12909, 813	1479
Neurokinin$_1$	^{3}H-Sar^{9}SP	CHO	Sar^{9}SP, 1.00	>10,000
Neurokinin$_2$	^{125}I-NKA	CHO	β-Ala NKA, 9.77	>10,000
Neurokinin$_3$	^{125}I-NKB	CHO	Me Phe^{7}NKB, 9.77	>10,000
Opiate δ	^{3}H-DPDPE	CHO-K1	Naloxone, 79.4	>10,000
Opiate κ	^{3}H-Naloxone	CHO-K1	Naloxone, 0.631	>10,000
Opiate μ	^{3}H-Naloxone	CHO-K1	Naloxone, 0.759	>10,000
Muscarinic M_1	^{3}H-N-methylscopolamine	CHO	Atropine, 4.68	4898
Muscarinic M_2	^{3}H-N-methylscopolamine	CHO	Atropine, 11.0	3311
Muscarinic M_3	^{3}H-N-methylscopolamine	CHO	Atropine, 10.7	>10,000
Muscarinic M_4	^{3}H-N-methylscopolamine	CHO	Atropine, 10.0	8318
Muscarinic M_5	^{3}H-N-methylscopolamine	CHO	Atropine, 6.31	>10,000

The displacement curves were established with eight concentrations (10-fold dilution steps) of iloperidone. Each concentration was tested in duplicate. The K_I values are the mean value of three separate experiments. For clarity, SEM-values are omitted since the variation was within 5% of the mean. [a]Where an internal reference is given, each assay was performed along with a full dose response curve of an internal reference compound to authenticate the quality.

thawed and homogenized just before the assay. Membranes expressing recombinant 5-HT_7 (Sf9 cells with baculovirus expression) were prepared by the Biotechnology Dept, Novartis Pharma, Basel, Switzerland.

The following membrane preparations were purchased from NEN Life Science Products, USA: NIH 3T3 cells expressing recombinant CCK_A and CCK_B; Sf9 cells expressing recombinant β_1 or β_2 receptors (all baculovirus expression); HeLa cells expressing recombinant 5-HT_6 receptors; and CHO cells expressing recombinant NK_1, NK_2, or NK_3 receptors. Other membrane preparations were purchased from Receptor Biology Inc: MDCK cells expressing recombinant norepinephrine transporter (hrNET); CHO cells expressing adenosine A_1, A_{2A} or A_3 receptors or muscarinic M_1, M_2, M_3, M_4 and M_5 receptors; HEK 293 cells expressing cannabinoid$_1$ receptors; CHO-K1 cells expressing recombinant dopamine transporter (hrDAT); and CHO-K1 cells expressing recombinant opiate δ, opiate μ and opiate κ receptors. Membranes from CHO-K1 cells expressing recombinant 5-HT_{1A} receptors were obtained from EuroScreen, SA.

Radioligand Binding Assays

96-well Microtiter Plate Filtration Assay. In general, the membrane preparations were homogenized after thawing and pretreated as required.

Individual radioligand binding assays for different receptors were performed as outlined by Herz et al. (1997) and references therein, with minor modifications if required. The binding studies were performed in 96-well plates (Falcon) in a total volume of 250 μL, consisting of the radioligand, drug (iloperidone or reference compound) and membrane preparation (cells, rat or guinea pig brain membranes) diluted in appropriate buffer. Non-specific binding was determined in the presence of an appropriate drug specific for the receptor under study. The plates were incubated at equilibrium for a specified time, as determined by kinetic experiments, for each receptor assay. Reactions were terminated by flash filtration and inverse transfer to 96-well filter plates (96-well cell harvester, filter plates GFC, coated with PAI as necessary, Canberra Packard). The plates were dried for 30 minutes at 56°C and sealed

Table 2. Affinity Profile of Iloperidone for Receptors for Which Human Homologue Was Unavailable

Receptor, species	Radioligand	Tissue	Internal reference, K_I (nM)[a]	Iloperidone K_I (nM)
Nicotine, rat	^{125}I-epibatidine	Brain	Epibatidine, 0.1	>10,000
Benzodiazepine, rat	^{3}H-Flunitrazepam	Brain	Diazepam, 4.67	12,882
Histamine H_1, guinea pig	^{3}H-Pyrilamine	Brain	Pyrilamine, 5.01	437
5-$HT_{1B/1D}$, bovine	^{125}I-GTI	Calf caudate		89.1

The displacement curves were established with eight concentrations (10-fold dilution steps) of iloperidone. Each concentration was tested in duplicate. The K_I values are the mean value of three separate experiments. For clarity, SEM-values are omitted since the variation was within 5% of the mean. [a]Where an internal reference is given, each assay was performed along with a full dose response curve of an internal reference compound to authenticate the quality.

at the bottom with an adhesive sheet (Topseal, Canberra Packard). Subsequently, 50 μL of scintillation fluid (Microscint-20, Canberra Packard) was added to each well, the plates sealed on top and the radioactivity counted in a 96-well plate counter (Topcount, Canberra Packard). The displacement curves were established with eight concentrations (10-fold dilution steps) of iloperidone. Each concentration was tested in duplicate. The K_I values are the mean value of three separate experiments.

Additional Binding Studies

Additional binding studies were performed in accordance with previously described methods: 5-$HT_{1B/1D}$ and 5-HT_7 (Bruinvels et al. 1992; Hoyer et al. 1997). Non-specific binding was determined in the presence of 10 μM 5-HT (5-HT_1 and 5-HT_7 sites).

Data Analysis

A standard data reduction algorithm was used to calculate percent specific binding in the presence of the test compound as follows:

$$([B - NSP]/[T - NSP]) \times 100$$

where: B = binding in the presence of test compound, NSP = non-specific binding in the presence of excess inhibitor, and T = total binding.

IC_{50} values were derived (where feasible) from a 4-parameter logistic fit and were converted to K_I values using the Cheng-Prusoff equation (Cheng and Prusoff 1973).

The entire data analysis was performed by a dedicated program linking the raw data to a custom driven Excel 7.0 macro and Graphpad Prism V 2.1. All affinities are expressed as K_I values (mol/L).

RESULTS

The derived *in vitro* receptor binding profile of iloperidone is included in Table 1 and Table 2. Iloperidone displayed moderate affinity (K_I 10–100 nM) at human α_{2C} adrenoceptors (16.2 nM), human D_{2A} (21.4 nM), human 5-HT_{1A} (93.1 nM), bovine 5-$HT_{1B/1D}$ (89.1 nM) and human 5-HT_6 receptors (63.1 nM). Low affinity (K_I 100–1000 nM) was observed at the human α_{2A} adrenoceptor (162 nM), human α_{2B} adrenoceptor (162 nM), guinea pig histamine H_1 (437 nM) and human 5-HT_7 receptors (112 nM). In addition, iloperidone had very low affinity (K_I 1000–10,000 nM) at the human CCK_B receptor, human dopamine and norepinephrine transporters, and human muscarinic M_1, M_2, M_4 receptors. There was no significant cross-reactivity ($K_I > 10$ μM) at all other receptors tested.

DISCUSSION

The affinity of iloperidone for a number of receptor sites considered important for antipsychotic activity has been reported previously (Szewczak et al. 1995; Kongsamut et al. 1996). The highest affinity was observed for the rat α_1-adrenoceptor (K_I 0.4 nM; Szewczak et al. 1995), while the compound also displayed a high affinity (K_I values below 10 nM) at the human recombinant 5-HT_{2A} receptor (K_I 5.6 nM), the short splice form (2B) of the human recombinant D_2 receptor (K_I 6.3 nM), and the D_3 receptor (K_I 7.1 nM; Kongsamut et al. 1996). These authors reported a K_I value of iloperidone for the long splice form of the human D_2 receptor of 13.3 nM, which is in good agreement with data obtained in the present study (21.4 nM). In addition, Kongsamut et al. (1996) reported a low affinity of iloperidone to receptors of the D_1 family: D_1 (K_I 216 nM) and D_5 (K_I 319 nM). The affinity for the 5-HT_{2C} receptor was reported as 42.8 nM.

The present study extends the radioligand binding profile of iloperidone with a large series of human receptors. A moderate affinity (K_I values between 10 and 100 nM) was observed for α_{2C} (K_I 16.2 nM), 5-HT_{1A} (93.1 nM) and 5-HT_6 (63.1 nM) receptors and bovine 5-$HT_{1B/1D}$ receptors (89.1 nM). Since antipsychotic compounds are dosed until a significant occupation (50–80%) of D_2 receptors is obtained (Nordström et al. 1993; Kapur et al. 2000), one can assume that therapeutic doses of iloperidone will result in relevant occupancy of D_3, 5-HT_{2A}, 5-HT_{2C}, α_1 and α_{2C} receptors. Whether 5-HT_{1A},

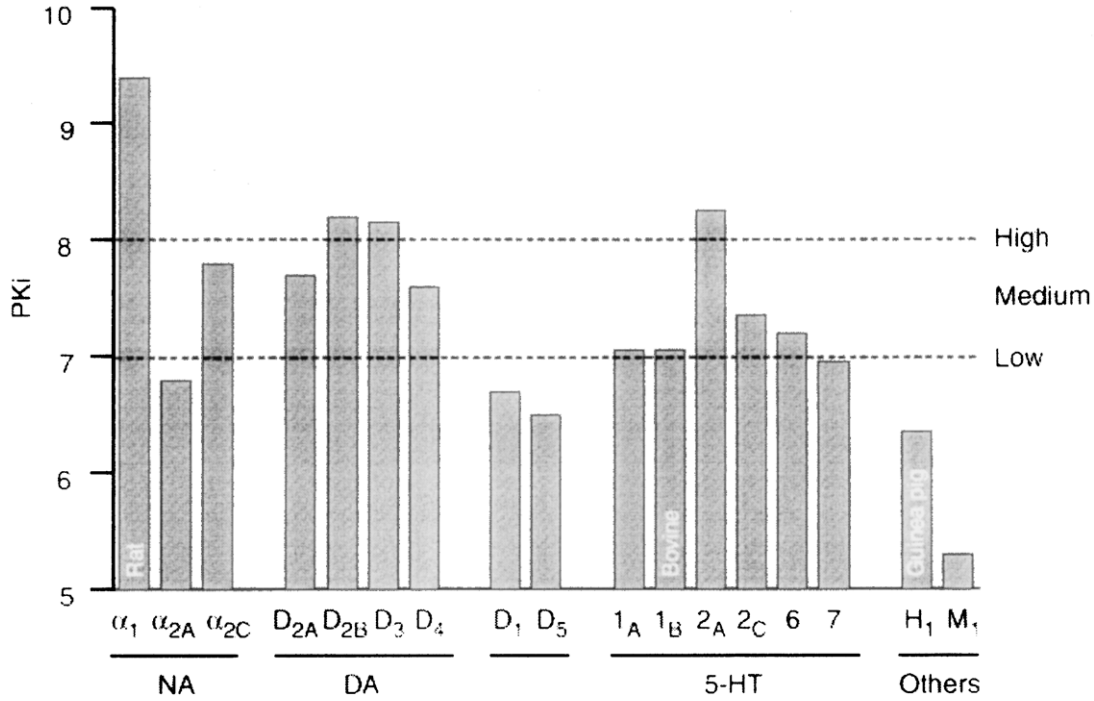

Figure 2. Bargraph of selected receptor affinities (pK_I in nM) of iloperidone. These affinities were measured at recombinant human receptors, with the exception of the α_1-adrenoceptor (rat), the 5-HT_{1B} receptor (bovine) and histamine H_1 receptor (guinea pig). The displacement curves were established with eight concentrations of iloperidone. Each concentration was tested three times. Variation was within 5% of the mean. Data for the α_1, the dopamine receptors, 5-HT_{2A} and 5-HT_{2C} receptor were reported previously (Kongsamut et al. 1996).

5-HT_{1B} and 5-HT_6 receptors will be occupied is less certain. At therapeutic doses, *in vivo* binding of iloperidone at receptors with lesser affinity (e.g. the adenosine family of receptors) would be negligible. The binding profile is summarized in graphical form in Figure 2. On the basis of this receptor binding profile one may predict some of iloperidone's clinical properties.

Overall Receptor Binding Affinity

Considering the present results in conjunction with those reported by Kongsamut et al. (1996), it is evident that iloperidone binds to three classes of monoamine receptor subtypes: dopamine, serotonin and norepinephrine receptors, but not to any other neurotransmitter receptor class. The moderate to high affinity of iloperidone for human D_2, 5-HT_{2A} and α_1 receptors suggest that iloperidone will have antipsychotic activity (Baldessarini et al. 1992; Willner 1997). Iloperidone's binding to 5-HT_{2C} and α_{2C} receptors will modify the therapeutic response and perhaps add additional therapeutic activity. On the other hand, iloperidone is devoid of affinity for receptor sites which are related to side effects (e.g. muscarine and histamine H_1 receptors). The potential relevance of each individual receptor site is discussed, roughly in order of declining affinity.

Affinity for α_1 Receptors

Three different subtypes of the human α_1-adrenoceptor (α_{1A}, α_{1B}, α_{1D}) have been identified by molecular cloning (Bylund 1992). The affinity of iloperidone to those α_1-adrenoceptor subtypes is not yet known. But since iloperidone displayed a very high affinity for rat brain α_1 adrenoceptors, it probably will have significant affinity for the human α_{1A}, α_{1B} and α_{1D} subtypes. Animal experiments provide circumstantial evidence that α_1 blockade might contribute to antipsychotic activity. For instance, prazosin administration to rats dose-dependently decreased burst firing and regularized the firing pattern of ventral tegmental dopamine neurons (Grenhoff and Svensson 1993). Disruption of prepulse inhibition by the psychotomimetic drug, phencyclidine, in rats (a putative model for the sensory motor gating deficit of schizophrenic patients), is normalized by α_1-adrenoceptor blocking antipsychotic compounds (Bakshi and Geyer 1997). These two preclinical experiments suggest that inappropriate α_1-adrenoceptor stimulation could

be involved in the pathogenesis of schizophrenia and α_1-adrenoceptor blockade could thus be a useful pharmacologic attribute for an antipsychotic compound. There are however, side effects such as postural hypotension that can occur through α_1-adrenergic blockade. Clinical studies have shown that clozapine frequently causes postural hypotension early in the course of treatment (Baldessarini and Frankenburg 1991). Iloperidone has shown similar effects early in treatment but tolerance is seen to develop as treatment continues (data on file).

Affinity for 5-HT$_{2A}$ Receptors

As indicated in the introductory section, iloperidone adheres to the theory put forward by Meltzer et al. (1989), in that it has a higher affinity for the 5-HT$_{2A}$ receptor than for the D_2 receptor. The theory predicts a better tolerability than classical antipsychotic compounds. Interestingly, the hallucinogen psilocybin induced schizophrenia-like psychosis in humans which was blocked by the selective 5-HT$_{2A}$ receptor antagonist, ketanserin (Vollenweider et al. 1998). Effective doses of psilocybin significantly decreased [^{11}C]raclopride binding in the striatum, which is indicative for an increase in endogenous dopamine levels in this brain structure (Vollenweider et al. 1999). Unexpected though, selective 5-HT$_{2A}$ receptor antagonists were not very effective in the treatment of psychoses in schizophrenia (Truffinet et al. 1999; Hoechst Marion Roussel, Company Press Release, 1999). Nevertheless, if combined with D_2 receptor blockade, 5-HT$_{2A}$ blockade might still represent a useful pharmacologic principle.

Morisset et al. (1999) have proposed that central 5-HT$_{2A}$ receptor blockade could represent a mechanism for improved cognition. The authors showed that antipsychotics with high 5-HT$_{2A}$ receptor antagonist affinity, including iloperidone, stimulated histamine neuron activity, which enhances alertness via H_1 receptor activation.

Affinity for D_{2A}, D_{2B}, D_3 and D_4 Receptors

According to their different pharmacologic profile and intracellular signaling pathways, dopamine receptors have traditionally been classified into two major populations, designated D_1 and D_2. Molecular cloning techniques have identified additional subtypes of dopamine receptor whose profiles suggest them to be members of either the D_1 or D_2 families (Sokoloff and Schwartz 1995). Thus, the cloned D_5 receptor resembles the classical D_1 receptor in being positively coupled to cAMP production and also in terms of sequence homology and the absence of introns. On the other hand, the D_3 and D_4 subtypes most closely resemble the D_2 receptor in being inhibitory on cAMP production and having a similar intron distribution (Sokoloff and Schwartz 1995). Alternative splicing of the D_2 receptor produces a long (D_{2A}) and a short (D_{2B}) variant in humans (reviewed by Sokoloff and Schwartz 1995). The D_2 family of receptors has been strongly linked to both the beneficial and side effects associated with antipsychotic agents. Attempts to divorce therapeutic benefit from adverse effects were given great impetus by reports that clozapine bound with high affinity and some selectivity to the dopamine D_4 over D_2 receptor subtypes (Van Tol et al. 1991). High affinity antagonists with marked selectivity have now been synthesized and, in some cases, examined in schizophrenic patients. No therapeutic efficacy was apparent (Kramer et al. 1997; Truffinet et al. 1999). These results indicate that D_4 receptor blockade is unlikely to be a major contributor to antipsychotic activity. Although iloperidone displayed relevant affinity for the human D_4 receptor (K_I 25 nM; Kongsamut et al. 1996), this probably has no therapeutic consequence.

Iloperidone, like most commonly used antipsychotics, has significant affinity for the dopamine D_3 receptor and is likely to interact at these sites at therapeutically relevant doses. Selective D_3 receptor antagonists have been described, but these are not yet tested in schizophrenic patients. Based on the pattern of expression of the D_3 receptor, this subtype could, however, be relevant for antipsychotic activity. The D_3 receptor is mainly expressed in mesocorticolimbic projection areas such as the medial forebrain bundle, the shell of the nucleus accumbens, olfactory tubercle, amygdala and cortical structures, but less in the nigrostriatal and tuberoinfundibular dopamine systems (Bouthenet et al. 1991).

Finally, differences in affinity for the two splice forms of the human D_2 receptor have also attracted attention (Malmberg et al. 1993; Usiello et al. 2000). Whereas most antipsychotic compounds display equal affinity for both variants, clozapine and remoxipride, two compounds with a low propensity to cause EPS, bound with higher affinity to the D_{2B} than to the D_{2A} form of the receptor. Usiello et al. (2000) found that the cataleptic effect of the typical antipsychotic haloperidol was absent in D_{2A} receptor deficient mice. These authors suggested that therapeutic activity could be related to blockade of presynaptic D_{2B} receptors, whereas extrapyramidal side effects could be avoided if the compound would fail to bind to D_{2A} receptors. As published by Kongsamut et al. (1996), iloperidone displays higher affinity for the D_{2B} than for the D_{2A} form which, according to the foregoing, would indicate a reduced propensity to cause EPS.

Affinity for α_{2A} and α_{2C} Adrenoceptors

Iloperidone's next highest affinity is to the norepinephrine α_{2C} binding site. Clozapine displays nanomolar affinity for the α_{2C} adrenoceptor (K_I 9.1 nM) and some se-

lectivity relative to the α_{2A} subtype (K_I 50 nM) (Schotte et al. 1996). It has been speculated that clozapine's superior therapeutic activity is at least partly explained by α_2-adrenoceptor blockade (Nutt 1994; Litman et al. 1996; Hertel et al. 1999). Other therapeutic effects of clozapine may also be related to α_2-adrenoceptor blockade. In monkeys with MPTP-induced Parkinsonism, dyskinetic movements induced by L-dopa were diminished by idazoxan, an α_2 antagonist (Henry et al. 1999; Grondin et al. 2000). Thus, blockade of α_2-adrenergic receptors could explain the potent antidyskinetic effect of clozapine (Bennett et al. 1994; Pierelli et al. 1998). Experiments in genetically altered mice show that overexpression of α_{2C} receptors contributes to behavioral despair and accordingly, blockade of α_{2C} receptors could be antidepressive (Sallinen et al. 1999). Other preclinical studies indicate that overexpression of α_{2C} receptors worsens spatial recognition and induces anxiety-like behavior (Björklund et al. 1998, 1999). These effect were reverted by an α_2 antagonist, suggesting that blockade of α_{2C} receptors might result in improved cognition and anxiolytic activity. On the other hand, also undesired properties may be related to blockade of α_2-adrenoceptors. Idazoxan and other α_2 antagonists are proconvulsant in mice (Jackson et al. 1991). Such an effect was not seen in a mutant mice strain that lacked functional α_{2A} receptors (Janumpalli et al. 1998), suggesting that proconvulsant activity is related to blockade of α_{2A} adrenergic receptors.

Iloperidone has a low affinity for α_{2A} receptors indicating a low propensity to induce convulsions. In contrast, the affinity of iloperidone for α_{2C}-adrenoceptors could be of clinical relevance as it might result in antidepressant and anxiolytic activity and in improved cognition.

Affinity for 5-HT$_{2C}$ Receptors

Recent research has shown that the 5-HT$_{2C}$ antagonist, SB206,553 dose-dependently increased the firing rate of VTA and locus coeruleus (LC) adrenergic neurons in rats (Gobert et al. 2000). These authors also reported that the 5-HT$_{2C}$ antagonist dose-dependently increase levels of dopamine (DA) and noradrenaline (NA) but not serotonin in the frontal cortex. Clozapine has been shown to preferentially increase dopamine release in the medial prefrontal cortex (Moghaddam and Bunney 1990). Since clozapine is a potent 5-HT$_{2C}$ antagonist (Schotte et al. 1996), the effects of clozapine on dopamine release in the prefrontal cortex might be due, at least partly, to blockade of 5-HT$_{2C}$. Dopamine hypofunction in cortical dopamine projection has been suggested to be responsible for negative symptomatology (Davis et al. 1991). Iloperidone shows moderate affinity to the 5-HT$_{2C}$ receptors (K_I 42.8 nM; Kongsamut et al. 1996) which might lead to disinhibition of the VTA and LC neurons, enhanced cortical DA and NA in the frontal cortex and thus an effect against negative symptoms of schizophrenia.

Activation of 5-HT$_{2C}$ receptors by fenfluramine or mCPP suppresses food intake in laboratory animals. For this reason the blockade of 5-HT$_{2C}$ receptors is suspected to contribute to the hyperphagia and weight gain observed with antipsychotic treatment. Chronic treatment of rats with selective 5-HT$_{2C}$ receptor antagonists did not lead to weight gain (Kennett et al. 1997). Also the antipsychotic drug ziprasidone displays relevant 5-HT$_{2C}$ blockade (Schotte et al. 1996), but did not induce profound weight gain in humans (Allison et al. 1999). Thus, although 5-HT$_{2C}$ receptor agonists induce hypophagia, the opposite is not necessarily observed with antagonists. Also iloperidone, despite its affinity for 5-HT$_{2C}$ receptors, produced, if compared to placebo, minimal weight gain in schizophrenic patients (data on file).

Selective 5-HT$_{2C}$ receptor antagonists displayed anxiolytic activity (Kennett et al. 1996, 1997) and suppressed haloperidol-induced catalepsy (Reavill et al. 1999). On theoretical grounds, 5-HT$_{2C}$ receptor antagonists might also be useful for the treatment of Parkinson's disease (Fox and Brotchie 1999). Iloperidone's affinity for 5-HT$_{2C}$ receptors could, therefore help to explain the low propensity to induce catalepsy and the anxiolytic effects seen in animal studies (Corbett et al. 1993).

Affinity for 5-HT$_6$ Receptors

The relevance of 5-HT$_6$ receptor blockade in the pharmacologic profile of antipsychotic compounds remains speculative. Roth et al. (1994) reported that clozapine and several atypical antipsychotic agents (rilapine, olanzapine, tiospirone, fluperlapine, clorotepine and zotepine) had high affinities for the 5-HT$_6$ receptor. It is interesting that selective 5-HT$_6$ receptor antagonist, Ro 04-6790 in rats increased cholinergic neurotransmission (Bentley et al. 1999). Similarly, clozapine, which has relevant 5-HT$_6$ receptor affinity (Glatt et al. 1995; Schotte et al. 1996), increased extracellular levels of acetylcholine in rat prefrontal cortex (Parada et al. 1997). It is therefore conceivable that clozapine increases extracellular levels of acetylcholine via blockade of 5-HT$_6$ receptors. Blockade of 5-HT$_6$ receptors could thus, via increased cholinergic neurotransmission, contribute to improved cognitive function. The present results show that iloperidone has moderate affinity for 5-HT$_6$ receptors, while the affinity for muscarine receptors is low. These two features in combination suggest that iloperidone could display efficacy against neurocognitive deficits in patients with schizophrenia. However, it is not certain whether therapeutic doses of iloperidone will be high enough to obtain significant occupancy of the 5-HT$_6$ receptor, as its affinity measured in the present experiments is rather moderate (K_I 63.1 nM).

Affinity for 5-HT$_{1A}$ Receptors

The same argument holds for the 5-HT$_{1A}$ receptor since the affinity of iloperidone for human 5-HT$_{1A}$ receptors amounted to 93.1 nM, only. In a cellular assay, iloperidone produced a concentration-dependent surmountable antagonism against the 5-HT$_{1A}$ receptor agonist, 8-OH-DPAT (mean [S.E.M.] pK$_B$ 7.69 [0.18]; data on file).

Post-mortem studies of patients with schizophrenia have revealed increased numbers of 5-HT$_{1A}$ receptors in the prefrontal cortex (Hashimoto et al. 1993; Burnet et al. 1997). Intrinsic activation of these receptors hyperpolarizes the neurons and reduces the output of their neurotransmitter glutamate. Loss and/or hypoactivity of cortical glutamatergic neurons has been postulated to underlie the cognitive impairment in Alzheimer's disease (Francis et al. 1993). Therefore, the normalization of glutamate output by a 5-HT$_{1A}$ antagonist such as iloperidone might help to ameliorate cognitive impairment in patients with schizophrenia.

Affinity for Muscarinic Receptors

The low or negligible affinity of iloperidone for muscarinic receptors indicates that it may have a low propensity to cause side effects such as dry mouth, blurred vision, increased frequency of micturition or other anticholinergic effects.

Affinity for Histamine H$_1$ Receptors

It is remarkable that antipsychotic drugs with high affinity for histamine H$_1$ receptors, like clozapine, olanzapine or thioridazine cause profound increases in body weight, whereas compounds with smaller H$_1$ affinity are less active in this respect (Allison et al. 1999). Also other compounds with high H$_1$ receptor affinity like the antidepressant mirtazapine (Fawcett and Barkin 1998), the antihypertensive ketanserin (Brogden and Sorkin 1990), or the migraine prophylactic pizotifen (Cleland et al. 1997) induce significant weight gain. These clinical observations are supplemented by preclinical studies showing that application of H$_1$ receptor antagonists or depletion of histamine elicits a feeding response (Doi et al. 1994). Iloperidone displays low affinity for the histamine H$_1$ receptor and indeed has shown little effect on body weight of schizophrenic patients (data on file).

Affinity for Other Receptors

The affinity of iloperidone for other receptors such as the 5HT$_3$ and nicotine cholinergic receptors is less than 10 μM (pK$_I$ $<$ 5.0), indicating that iloperidone is inactive at these sites.

CONCLUSION

Iloperidone is characterized by a broad spectrum of dopamine, norepinephrine and serotonin antagonism. Thus, as with other new antipsychotics, iloperidone has a high affinity for 5-HT$_{2A}$ receptors and α_1 adrenergic receptors and moderate affinity for D$_2$ receptors, indicating antipsychotic efficacy, with a reduced propensity to induce EPS. Favourable properties are also suggested by its additional receptor profile. The moderate D$_2$ receptor affinity is balanced by comparable affinity for α_{2C} adrenoceptors, and 5-HT$_{2C}$, suggesting potential improvements in cognition and negative symptoms. Moreover, blockade of α_{2C} adrenoceptors might translate into antidepressant and anxiolytic activity. Low affinity for histamine H$_1$ receptors suggests that iloperidone has limited propensity to induce weight gain. Extremely low activity at cholinergic receptors suggests that side effects associated with anticholinergic agents such as dry mouth, blurred vision and increased frequency of micturition will be avoided. Due to the low affinity of iloperidone for α_{2A} receptors proconvulsive activity is not expected.

This broad receptor binding profile indicates that iloperidone has the potential to be an effective and well-tolerated agent in the treatment of psychotic disorders. Indeed, preliminary studies have confirmed the favourable efficacy and tolerability of iloperidone in patients with schizophrenia (Davidson et al. 1994; Borison et al. 1996; Cutler et al. 1996).

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