ELSEVIER

European Journal of Pharmacology 317 (1996) 417–423

ejp

Short communication

Iloperidone binding to human and rat dopamine and 5-HT receptors

Sathapana Kongsamut *, Joachim E. Roehr, Jidong Cai, Harold B. Hartman, Paul Weissensee, Lisa L. Kerman, Lei Tang, Anthony Sandrasagra

Neuroscience Research, Hoechst Marion Roussel, Inc., Route 202-206, P.O. Box 6800, Bridgewater, NJ 08807-0800, USA

Received 1 October 1996; accepted 22 October 1996

Abstract

Iloperidone (HP 873; 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone) is a compound currently in clinical trials for the treatment of schizophrenia. Iloperidone displays affinity for dopamine D_2 receptors and for 5-HT_{2A} receptors and has a variety of in vivo activities suggestive of an atypical antipsychotic. Here we present an examination of the affinity of iloperidone to a variety of human and rat homologs of dopamine and 5-HT receptor subtypes. We employed receptor binding assays using membranes from cells stably expressing human dopamine D_1, D_{2S}, D_{2L}, D_3, D_4 and D_5 and 5-HT_{2A} and 5-HT_{2C} receptors and rat 5-HT_6 and 5-HT_7 receptors. Iloperidone displayed higher affinity for the dopamine D_3 receptor ($K_i = 7.1$ nM) than for the dopamine D_4 receptor ($K_i = 25$ nM). Iloperidone displayed high affinity for the 5-HT_6 and 5-HT_7 receptors ($K_i = 42.7$ and 21.6 nM, respectively), and was found to have higher affinity for the 5-HT_{2A} ($K_i = 5.6$ nM) than for the 5-HT_{2C} receptor ($K_i = 42.8$ nM). The potential implications of this receptor binding profile are discussed in comparison with data for other antipsychotic compounds.

Keywords: Dopamine receptor; 5-HT receptor; Schizophrenia; Psychotic disorder; Antipsychotic agent

1. Introduction

Iloperidone (HP 873; 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]-ethanone) is a new atypical antipsychotic agent currently in clinical trials for the treatment of schizophrenia (Borison et al., 1995). It was selected for development based on its affinity for rat dopamine D_2 and 5-HT_2 receptors and on its favorable profile in a variety of other biochemical and behavioral tests (Corbett et al., 1993; Strupczewski et al., 1995; Szewczak et al., 1995; Szczepanik et al., 1996).

Schizophrenia is a serious, chronic, psychiatric disease affecting approximately 1% of the world's population and having profound effects, personally and financially, on patients and their families. A person with schizophrenia suffers from symptoms broadly categorized as 'positive', 'negative' and 'cognitive'. Positive symptoms include delusions, hallucinations and disorganization of thought. Negative or deficit symptoms include social withdrawal, impairment in role functioning, flat affect, poverty of speech, marked lack of initiative or energy, and inability to experience pleasure. Cognitive symptoms comprise impairments in attention, verbal fluency, recall memory and executive function. These symptoms make it extremely difficult for the schizophrenic patient to function normally within society.

Since the correlation between antagonism of dopamine receptors, specifically of the D_2 subtype, and clinical antipsychotic activity against positive symptoms was made (see Creese et al., 1978), a large number of agents with varied chemical structures have been created and are used in the treatment of schizophrenia and related disorders. These agents have varying degrees of clinical efficacy against positive symptoms of schizophrenia and this efficacy is correlated with antagonism of dopamine D_2 receptors in mesolimbic/mesocortical brain regions (see, for example, Davis et al., 1991). In contrast, antagonism of dopamine D_2 receptors in the corpus striatum is correlated with acute Parkinson-like extrapyramidal symptoms, notably dystonia (involuntary muscle spasms), pseudoparkinsonism (tremor and rigidity) and akathisia (restlessness). Following long-term chronic treatment with these agents, there is a risk of developing tardive dyskinesia (for review, see Baldessarini, 1996). Thus, most of the currently available antipsychotic agents, while effective, are associated with a high incidence of extrapyramidal symp-

* Corresponding author. Tel.: (1-908) 231-3072; Fax: (1-908) 231-4335; e-mail: KONGSAM1@brwhcc3.hcc.com

toms, leading to low patient compliance and high relapse/rehospitalization rates.

Recently, it has been suggested that agents which antagonize 5-HT_2 receptors in the brain, along with dopamine D_2 receptors, may have an improved ratio of therapeutic effect to extrapyramidal symptoms (see Bersani et al., 1986; Stockmeier et al., 1993). Examples of such compounds are clozapine and risperidone. The property of antagonizing both dopamine D_2 and 5-HT_2 receptors may contribute to reduced extrapyramidal symptom liability of these compounds at doses that effectively treat schizophrenic symptoms (Janssen et al., 1988; Leysen et al., 1988; Meltzer, 1989). A number of other agents with this mechanism of action are in varying stages of development. Of note among these are olanzapine and seroquel, which are structural analogs of clozapine (Bymaster et al., 1996; Saller and Salama, 1993). Widespread use of clozapine has been limited by the significant (approximately 1%) incidence of agranulocytosis.

The application of molecular biological tools has enabled the cloning and expression of a number of novel dopamine and serotonin receptors (see Jarvie and Caron, 1993; Hoyer et al., 1994). The functions of these receptors are currently being intensively explored. Of note among these studies is the differing affinity for dopamine D_2-like receptors (D_3 and D_4) that may explain some of the variability in efficacy seen among known antipsychotic agents (see, for example, Schwartz et al., 1992). Additionally, affinity for 5-HT_6 receptors may be associated with reduced propensity for extrapyramidal symptoms (Roth et al., 1994) and affinity for 5-HT_{2C} receptors may be responsible for neuroleptic-induced weight gain. Transgenic mice in which the expression of the 5-HT_{2C} has been blocked are obese (Tecott et al., 1995) suggesting that inhibiting this receptor with a drug may produce weight gain.

We report here investigations on the affinity of iloperidone and selected other antipsychotic agents for cloned dopamine and serotonin receptor subtypes. We discuss these results with special reference to known or suspected functions of these receptors and, based on these results and suspected functions, make conclusions for clinical efficacy and side effect liability of iloperidone.

2. Materials and methods

2.1. Receptor cloning and expression

2.1.1. Dopamine D_1 and D_5 receptors

The human dopamine D_1 and D_5 cDNAs were obtained from the laboratory of Dr. Marc Caron in the vector pCMV5. The coding regions of the human D_1 and D_5 receptors were subcloned into pMMLV (Sandrasagra et al., unpublished) and pRC/RSV (Invitrogen), respectively. Chinese hamster ovary (CHO) cells were then transfected with these constructs and geneticin (G418)-resistant clones were isolated. Clonal cell lines expressing high levels of the receptors (as determined by mRNA and receptor binding data) were chosen and characterized pharmacologically.

2.1.2. Dopamine D_{2S} and D_{2L} receptors

The dopamine D_2 receptor gene was isolated from a human striatal (caudate/putamen) cDNA library; short and long splice variants, D_{2S} and D_{2L}, were sequenced and sub-cloned into the expression vector pRC/RSV (Invitrogen). CHO cells were stably transfected and G418 resistant clones were isolated. Using mRNA and binding data, single high expressing clones were identified, and these clones were pharmacologically characterized.

2.1.3. Dopamine D_3 and D_4 receptors

Membranes from CCL1.3 cells stably expressing the human dopamine D_3 receptor were obtained from Research Biochemicals International (Natick, MA, USA). Membranes from CHO cells stably expressing the human dopamine D_4 receptor ($D_{4.7}$ isoform) were obtained from Dr. J. Baumgold (Receptor Biology, Baltimore, MD, USA).

2.1.4. 5-HT_{2A} and 5-HT_{2C} receptors

The 5-HT_{2A} and 5-HT_{2C} receptor genes were isolated from human substantia nigra and human cerebral cortex libraries, respectively. Each gene was sequenced and subcloned into the expression vector pRC/RSV (Invitrogen). Baby hamster kidney (BHK) and CHO cells were stably transfected with the 5-HT_{2A} and 5HT_{2C} receptor cDNAs, respectively, and G418 resistant clones were isolated. Clones expressing high levels of the receptors (as determined by mRNA and receptor binding data) were chosen and pharmacologically characterized.

2.1.5. Serotonin 5-HT_6 and 5-HT_7 receptors

Membranes from CHO cells stably expressing the rat 5-HT_6 and 5-HT_7 receptor were obtained from Dr. J. Baumgold (Receptor Biology, Baltimore, MD, USA).

2.2. Cell culture conditions

2.2.1. Adherent cultures

Adherent CHO cultures were grown in 150 mm plates or roller bottles using the following medium: Ham's F-12 with 10% fetal bovine serum, 400 μg/ml G418 and penicillin-streptomycin (100 U/ml and 100 μg/ml). Cells were grown to confluence and were harvested by mechanical scraping.

2.2.2. Suspension cultures

Suspension cultures were employed for CHO cells expressing dopamine D_1 and D_{2L} receptors. Cells were initially grown on plates and were transferred to suspension culture at 300 000 cells/ml in medium containing

50% CHO-SFM-II, 50% Ham's F-12 containing 10% fetal bovine serum (final conc. 5%), 400 μg/ml G418 and penicillin/streptomycin (100 U/ml and 100 μg/ml; all from Gibco). Growth was monitored and cell viability was assessed using trypan blue exclusion. Viable cell density was maintained at between 300 000 and 600 000 cells/ml, and serum was gradually withdrawn by reducing the percentage of Ham's F-12 containing fetal bovine serum.

2.3. Membrane preparation

Cells from both adherent and suspension were harvested into 250 ml centrifuge tubes and spun down at $1200 \times g$. The medium was removed, cells were then washed with 100 ml phosphate-buffered saline, resuspended in water, and homogenized with a polytron on ice at a medium setting. The homogenate was spun down and resuspended in distilled water in order to reduce clumping and to maintain the homogenate as membrane fragments. Following protein determination, the membrane homogenate was diluted with 10% dimethyl sulfoxide and stored in cryogenic vials at −80°C until used.

2.4. Protein determination

For determination of membrane protein, the membrane suspension was diluted 1:1 with 1% sodium dodecyl sulfate, vortexed and allowed to stand for 5 min. This solubilized protein was measured using the BioRad DC protein determination kit (Catalog No. 500-0112). Protein concentrations were calculated by linear regression and interpolation based on a standard curve using bovine serum albumin as standard.

2.5. Receptor binding assays

All assays were conducted at 37°C in a Tris buffer containing salts (50 mM Tris buffer, pH 7.7; 120 mM NaCl; 5 mM KCl; 2 mM $CaCl_2$; 1 mM $MgCl_2$), with the exception of the 5-HT_{2C} receptor assay where a different buffer was used (50 mM Tris, 4 mM $CaCl_2$ and 1% ascorbate, pH 7.4). Various binding parameters (ligand, ligand concentration, incubation times, ligand K_d values, displacing agent to define specific binding and tissue/cell line used) are summarized in Table 1. Except where indicated, all binding parameters were optimized at Hoechst Marion Roussel; ligand K_d values were determined using both saturation analysis (Scatchard) as well as kinetic analysis (association and dissociation rates). Membranes from rat tissues were freshly prepared; cell membranes (previously prepared and frozen) were rapidly thawed. Membranes were diluted to an appropriate concentration (between 50–500 μg protein/assay point depending on receptor expression level) in Tris buffer and homogenized.

The tubes or plates were incubated at 37°C in a shaking water bath for the times indicated. The assay was stopped by rapid filtration through Whatman GF/B filters (presoaked in 0.3% polyethyleneimine) using a Brandel-48 Cell Harvester or Packard 96-well Cell Harvestor. The filter strips were then washed with 15 ml ice-cold 0.05 M Tris buffer, pH 7.7, and counted in 5 ml of Ecoscint (National Diagnostics) or 40 μl of Microscint (Packard) scintillation cocktail.

2.6. Data analysis

IC_{50} and K_i calculations were performed using nonlinear regression one-site competition analysis (GraphPad,

Table 1
Receptor binding parameters

Receptor	Ligand	Ligand concentration (nM)	Incubation time (min)	Ligand K_d (nM)	Non-specific	Cell/tissue
Rat D_1	[^{3}H]SCH23390	0.5	20	0.48	1 μM (+)-butaclamol	Whole striatum
Rat D_2	[^{3}H]Spiperone	0.4	20	0.8	2 μM (+)-butaclamol	Whole striatum
Rat 5-HT_2	[^{3}H]Spiperone	1.5	10	0.75	5 μM methysergide	Frontal cortex
Rat 5-HT_6 [a]	[^{3}H]LSD	5	60	2.3	10 μM clozapine	HEK 293
Rat 5-HT_7 [a]	[^{3}H]LSD	4	60	3.1	10 μM clozapine	HEK 293
Human D_1	[^{3}H]SCH23390	1	30	1.27	3 μM (+)-butaclamol	CHO
Human D_{2S}	[^{3}H]Spiperone	1	15	0.07	3 μM (−)-eticlopride	CHO
Human D_{2L}	[^{3}H]*N*-Methyl spiperone	0.4	30	0.1	3 μM (−)-eticlopride	CHO
Human D_3	[^{3}H]*N*-Methyl spiperone	0.4	30	0.2	3 μM (−)-eticlopride	CHO
Human D_4 [a]	[^{3}H]Spiperone	0.5	20	0.1	10 μM haloperidol	CHO
Human D_5	[^{3}H]SCH23390	0.3	30	0.31	1 μM (+)-butaclamol	CHO
Human 5-HT_{2A} [b]	[^{3}H]RP 62203	0.5	30	0.13	10 μM methysergide	BHK
Human 5-HT_{2C} [c]	[^{3}H]Mesulergine	1	30	1.9	100 nM mianserin	CHO

inc. = incubation; [a] receptor binding parameters obtained from Receptor Biology, Inc.; [b] parameters obtained from Malgouris et al. (1993); [c] parameters obtained from Canton et al. (1990). Assays were designed to be specific for the receptor population being measured. All Scatchard analyses with the ligands above showed a single site; displacement of the ligands was assumed to be single site displacements.

Prism), with top and bottom limits held constant at 0% and 100% inhibition, respectively. The percent inhibition at each drug concentration was the average of duplicate determinations. Except where indicated, each determination was performed 2–5 times.

3. Results

Results are presented in Table 2. Highlights from the table are summarized below.

3.1. Affinity for dopamine D_1 and D_5 receptors

Iloperidone had low affinity (K_i values in the 10^{-7} M range) for dopamine D_1 and D_5 receptors (rat and human). We found most antipsychotic compounds to have low affinity (high K_i values) for dopamine D_1 and D_5 receptors relative to their affinity for dopamine D_2 receptors. Exceptions to this are the tricyclic compounds, clozapine, olanzapine and seroquel, which had affinities for dopamine D_1 receptors in the same range (within 2-fold) as their affinities for dopamine D_2 receptors. This was seen with data for both rat and human receptors. Affinity for dopamine D_5 receptors was roughly equal to that for dopamine D_1 receptors.

3.2. Affinity for dopamine D_2-like receptors

In general, affinities for human dopamine D_2 receptors were found to be higher than those for rat dopamine D_2 receptors. There was no difference between affinity for dopamine D_{2S} and D_{2L} receptors. Clozapine showed selectivity for dopamine D_4 receptors over dopamine D_2 receptors. Olanzapine, seroquel and haloperidol each showed similar affinities for dopamine D_2, D_3 and D_4 receptors (albeit with different potencies), and risperidone and iloperidone showed somewhat greater affinity for dopamine D_2 over D_4 receptors (K_i ratios $D_4/D_2 = 3.3$ and 3.5, respectively). Unlike other compounds, iloperidone showed higher affinity for dopamine D_3 receptors over D_4 receptors.

3.3. D_2 / 5-HT_2 ratios

The rat D_2/5-HT_2 ratio of K_i values was 17.4 for iloperidone, 12.9 for clozapine and 14.3 for risperidone. For the other compounds, this ratio was less than 10; for haloperidol, the ratio was 0.3. When examined in human receptors, the human D_{2L}/5-HT_{2A} ratio of K_i values was 12.5 for clozapine, 1.1 for iloperidone, 2.45 for risperidone, 1.6 for olanzapine, 1.1 for seroquel and 0.012 for haloperidol.

3.4. Binding to 5-HT_{2A} and 5-HT_{2C} receptors

With the exception of seroquel and haloperidol, the compounds showed high affinity for the human 5-HT_{2A} receptor. Iloperidone and risperidone showed 7.6- and 11-fold selectivity for 5-HT_{2A} over 5-HT_{2C} receptors, respectively. Clozapine and olanzapine showed 2.2- and 3.8-fold selectivity for 5-HT_{2C} over 5-HT_{2A} receptors, respectively.

3.5. Binding to 5-HT_6 and 5-HT_7 receptors

Iloperidone and clozapine showed high affinity for 5-HT_6 and 5-HT_7 receptors. Risperidone, seroquel and haloperidol had K_i values for binding to 5-HT_6 receptors of greater than 1000 nM. Risperidone had sub-nanomolar affinity for the 5-HT_7 receptor. K_i values for olanzapine, seroquel and haloperidol at 5-HT_7 receptors were greater than 100 nM.

Table 2
Binding affinities (K_i values in nM ± S.E.) of iloperidone and selected antipsychotic agents for various rat and human dopamine and 5-HT receptors

	Iloperidone	Risperidone	Clozapine	Olanzapine	Seroquel	Haloperidol
Rat D_1	546 ± 80 [a]	550 ± 70 [a]	690 ± 80 [a]	100 ± 5	2610 ± 20	520 ± 100 [a]
Rat D_2	54 ± 8 [a]	20 ± 1 [a]	790 ± 100 [a]	52.3 ± 31.7	329 [b]	13 ± 2 [a]
Rat 5-HT_{1A}	168 ± 20 [a]	570 ± 100 [a]	640 ± 100 [a]	4546 [c]	720 [b]	> 2000 [a]
Rat 5-HT_2	3.1 ± 2 [a]	1.4 ± 0.9 [a]	61 ± 40 [a]	13.3 ± 1.4	185 [c]	45 ± 9 [a]
Rat 5-HT_6	42.7 ± 35.4	1122 ± 514	7.1 ± 2.0	27.5 ± 18.9	1297 ± 943	3683 ± 59
Rat 5-HT_7	21.6 ± 10.5	0.93 ± 0.67	19.1 ± 4.7	152.2 ± 32.6	133.6 ± 47.4	241.2 ± 143.7
Human D_1	216 ± 34	523 ± 68	196 ± 28	35 [c]	1277 ± 334	82 ± 7
Human D_{2S}	13.3 ± 3.5	3.3 ± 0.3	168 ± 38	30.3 ± 5.7	779 ± 104	2.1 ± 1.2
Human D_{2L}	6.3 ± 1.5	2.7 ± 0.4	291 ± 93	37.7 ± 4.1	706 ± 101	2.3 ± 1.3
Human D_3	7.1 ± 4.1	14.1 ± 4.8	473 ± 490	49 ± 28	839 ± 256	1.9 ± 0.3
Human D_4	25 ± 0.3	9 ± 1.9	54.5 ± 7.5	29.5 ± 2.5	1057 ± 1	3 ± 0.06
Human D_5	319 ± 131	563 ± 127	281 ± 64	74 ± 13	1513 ± 407	178 ± 9
Human 5-HT_{2A}	5.6 ± 0.3	1.1 ± 0.2	23.2 ± 2.3	24.2 ± 5.7	636 ± 34.5	186 ± 79
Human 5-HT_{2C}	42.8 ± 1.6	12 ± 0.2	10.7 ± 0.3	6.4 ± 0.01	1184 ± 266	3949 ± 67

[a] Values from Corbett et al. (1993); [b] IC_{50} values from Saller and Salama (1993); [c] single determination in triplicate.

4. Discussion

Iloperidone was selected as an atypical antipsychotic compound based in part on its affinity for rat dopamine D_2 and 5-HT_2 receptors. In the current work, iloperidone exhibited high affinity for human dopamine D_2 and D_3 and for 5-HT_{2A} receptors. Iloperidone also exhibited high affinity for dopamine D_4, and for 5-HT_{2C}, 5-HT_6 and 5-HT_7 receptors. However, iloperidone displayed low affinity for dopamine D_1 and D_5 receptors. This receptor binding profile may predict pharmacological activities discussed below.

4.1. Affinity for dopamine D_2 receptors and clinical potency

Iloperidone is among the most potent antipsychotic compounds: it has low nanomolar affinity for dopamine D_2 receptors, comparable to haloperidol and risperidone, two known potent compounds. This characteristic is correlated with the low doses used in the clinic: 8 mg/day for iloperidone (Borison et al., 1995), 2–20 mg/day for haloperidol and 2–8 mg/day for risperidone (Baldessarini, 1996). Olanzapine also has high affinity for the dopamine D_2 receptor and is a potent compound being used at 10 mg/day (Beasley et al., 1996). By comparison, clozapine is used at doses of approximately 350 mg/day (Baldessarini, 1996).

Affinity for α_1-adrenoceptors has also been suggested to play a role in the efficacy of antipsychotic compounds (Baldessarini et al., 1992). Iloperidone has relatively high affinity for α_1-adrenoceptors (Sainati et al., 1995).

4.2. Efficacy against negative symptoms

Corbett et al. (1993) predicted, based on its D_1/5-HT_{1A} ratio of affinities and behavioral measures, that iloperidone would have efficacy against negative symptoms. This has been observed in the clinic (see Borison et al., 1995). Clozapine and risperidone also showed appropriate activity in the D_1/5-HT_{1A} ratio and in the rat social interaction test (Corbett et al., 1993).

Antagonist activity at the 5-HT_{2A} receptor has also been suggested to predict efficacy against negative symptoms (see, for example, Leysen et al., 1993; Rao and Möller, 1994). The high affinity of iloperidone for 5-HT_{2A} receptors indicates that it should have efficacy against negative symptoms.

4.3. Liability for extrapyramidal symptoms

The D_2/5-HT_2 ratio of K_i values has been suggested to be a predictor of liability for extrapyramidal symptoms (Janssen et al., 1988; Leysen et al., 1988; Meltzer, 1989), that is, a high ratio predicts low extrapyramidal symptom liability. When receptor binding data from rat membranes are examined, the D_2/5-HT_2 ratio of K_i values was 17.4 for iloperidone, 12.9 for clozapine and 14.3 for risperidone. For the other compounds, this ratio was less than 10. For haloperidol, the ratio was 0.3. When examined in human receptors, the human D_{2L}/5-HT_{2A} ratio of K_i values was 12.5 for clozapine, 1.1 for iloperidone, 2.45 for risperidone, 1.6 for olanzapine, 1.1 for seroquel and 0.012 for haloperidol. Interestingly, in rats, iloperidone and risperidone have ratios comparable to clozapine. Nevertheless, iloperidone, risperidone, olanzapine and seroquel are significantly different from haloperidol, whose human D_{2L}/5-HT_{2A} ratio is more than 10-fold lower than its rat D_2/5-HT_2 ratio.

The difference between the human and rat D_2/5-HT_2 ratios is striking. It is particularly interesting that clozapine maintains the high ratio, and that the ratio for all the other compounds is decreased in human vs. rats. This difference may be due to some technical aspect of the rat binding assays. For example, the rat assays are not performed using clonal cell lines expressing the rat receptors, a question that can be addressed in further studies. Alternatively, they may be due to true species differences in the receptor populations. If the latter is true and we believe in the theory that the D_2/5-HT_2 ratio is a good predictor of extrapyramidal side effects, then the newer antipsychotic compounds ought to be different from clozapine in this aspect of their overall profile.

A second predictor of low extrapyramidal symptom liability may be affinity for the 5-HT_6 receptor: high affinity for this receptor has been suggested to be correlated with low extrapyramidal symptom liability (Roth et al., 1994). This property distinguishes iloperidone, clozapine and olanzapine from risperidone, haloperidol and seroquel. Indeed, at the high end of the therapeutic dose range, risperidone does produce extrapyramidal symptoms (Owens, 1994). Iloperidone, with its higher affinity for 5-HT_6 receptors, would be predicted to produce less (or no) extrapyramidal symptoms.

Iloperidone exhibited low or no propensity for extrapyramidal symptoms in a number of animal models (Szewczak et al., 1995; Szczepanik et al., 1996) and in clinical studies (Borison et al., 1995).

4.4. Neuroleptic-induced weight gain

Transgenic mice in which expression of the 5-HT_{2C} receptor has been knocked out are obese (Tecott et al., 1995), suggesting that inhibition of signalling through this receptor, for example by drugs, could produce weight gain. Interestingly, clozapine has high affinity for 5-HT_{2C} receptors relative to dopamine D_2 receptors, and weight gain is a significant problem in its use (see, for example, Leadbetter et al., 1992). In contrast, haloperidol has low affinity for 5-HT_{2C} receptors and weight gain is less of a problem with this compound. Experience with the other compounds is still limited; however, the receptor binding profiles

(dopamine D_2 and 5-HT_{2A} vs. 5-HT_{2C}) would predict that risperidone and iloperidone would have fewer weight gain problems than clozapine. Olanzapine has higher affinity for 5-HT_{2C} receptors than for 5-HT_{2A} receptors and has been reported to produce weight gain (Beasley et al., 1996).

4.5. Summary

Iloperidone has a receptor binding profile different from any of the other antipsychotic agents studied. This profile, together with data from animal studies, previously reported (Corbett et al., 1993; Szewczak et al., 1995; Szczepanik et al., 1996) predict that iloperidone will be a potent antipsychotic with efficacy against positive and negative symptoms and low propensity to produce extrapyramidal symptoms. These properties are being observed in current clinical studies (Borison et al., 1995).

Acknowledgements

The authors would like to thank M. Nielen and T. Jessen for help with portions of the cloning and expression of the various receptors.

References

Baldessarini, R.J., 1996, Drugs and the treatment of psychiatric disorders, in: The Pharmacological Basis of Therapeutics, 9th edn., eds. J.G. Hardman, L.E. Limbird, P.B. Molinoff, R.W. Ruddon and A.G. Gilman, p. 399.

Baldessarini, R.J., D. Hulston-Lyons, A. Campbell, E. Marsh and B.M. Cohen, 1992, Do central antiadrenergic actions contribute to the atypical properties of clozapine?, Br. J. Pharmacol. 160 (Suppl. 17), 12.

Beasley, C.M., G. Tollefson, P. Tran, W. Satterlee, T. Sanger, S. Hamilton and the Olanzapine HGAD Study Group, 1996, Olanzapine versus placebo and haloperidol, acute phase results of the North American double-blind olanzapine trial, Neuropsychopharmacology 14, 111.

Bersani, G., A. Grispini, S. Marini, A. Pasini, M. Valducci and N. Ciani, 1986, Neuroleptic-induced extrapyramidal side-effects: clinical perspectives with ritanserin (R 55 667), a new selective 5-HT_2 receptor blocking agent, Curr. Ther. Res. 40, 492.

Borison, R.L., F.J. Huff, J. Veraklis, L. Griffiths, R. Ramaswamy and J. Shipley, 1995, Efficacy of 2 and 4 mg BID iloperidone (HP 873) administered to schizophrenic patients for 42 days, ACNP Abstr. 34, 135.

Bymaster, F.P., D.O. Calligaro, J.F. Falcone, R.D. Marsh, N.A. Moore, N.C. Tye, P. Seeman and D.T. Wong, 1996, Radioreceptor binding profile of the atypical antipsychotic olanzapine, Neuropsychopharmacology 14, 87.

Canton, H., L. Verriéle and F.C. Colpaert, 1990, Binding of typical and atypical antipsychotics to 5-HT_{1C} and 5-HT_2 sites: clozapine potently interacts with 5-HT_{1C} sites, Eur. J. Pharmacol. 191, 93.

Corbett, R., H.B. Hartman, L.L. Kerman, A.T. Woods, J.T. Strupczewski, G.C. Helsley, P.G. Conway and R.W. Dunn, 1993, Effects of atypical antipsychotic agents on social behavior in rodents, Pharmacol. Biochem. Behav. 45, 9.

Creese, I., D.R. Burt and S.H. Snyder, 1978, Biochemical actions of neuroleptic drugs: focus on the dopamine receptor, in: Handbook of Psychopharmacology, eds. L.L. Iversen, S.D. Iversen and S.H. Snyder, Vol. 10, p. 37.

Davis, K.L., R.S. Kahn, G. Ko and M. Davidson, 1991, Dopamine in schizophrenia: a review and reconceptualization, Am. J. Psychiatry 148, 1474.

Hoyer, D., D.E. Clarke, J.R. Fozard, P.R. Hartig, G.R. Martin, E.J. Mylecharane, P.R. Saxena and P.P.A. Humphrey, 1994, VII. International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin), Pharmacol. Rev. 46, 157.

Janssen, P.A.J., C.J.E. Niemegeers, F. Awouters, K.H.L. Schellekens, A.A.H.P. Megens and T.F. Meert, 1988, Pharmacology of risperidone (R 64 766), a new antipsychotic with serotonin-S_2 and dopamine-D_2 properties, J. Pharmacol. Exp. Ther. 244, 685.

Jarvie, K.R. and M.G. Caron, 1993, Heterogeneity of dopamine receptors, Adv. Neurol. 60, 325.

Leadbetter, R., M. Shutty, D. Pavalonis, V. Vieweg, P. Higgins and M. Downs, 1992, Clozapine-induced weight gain: prevalence and clinical relevance, Am. J. Psychiatry 149, 68.

Leysen, J.E., W. Gommeren, A. Eens, D. Dechaffoy de Cowicelles, J.C. Stoof and P.A.J. Janssen, 1988, Biochemical profile of risperidone, a new antipsychotic, J. Pharmacol. Exp. Ther. 247, 661.

Leysen, J.E., P.M.F. Janssen, A. Schotte, W.H.M.L. Luyten and A.A.H.P. Megens, 1993, Interaction of antipsychotic drugs with neurotransmitter receptor sites in vitro and in vivo in relation to pharmacological and clinical effects: role of 5-HT_2 receptors, Psychopharmacology 112, S40.

Malgouris, C., F. Flamand and A. Doble, 1993, Autoradiographic studies of RP 62203, a potent 5-HT_2 receptor antagonist, pharmacological characterization of [^{3}H]RP 62203 binding in the rat brain, Eur. J. Pharmacol. 233, 37.

Meltzer, H.Y., 1989, Clinical studies on the mechanism of action of clozapine: the dopamine-serotonin hypothesis of schizophrenia, Psychopharmacology 99, S18.

Owens, D.G., 1994, Extrapyramidal side effects and tolerability of risperidone: a review, J. Clin. Psychiatry 55 (Suppl.), 29.

Rao, M.L. and H.-J. Möller, 1994, Biochemical findings of negative symptoms in schizophrenia and their putative relevance to pharmacologic treatment, Neuropsychobiology 30, 160.

Roth, B.L., S.C. Craigo, M.S. Choudhary, A. Uluer, F.J. Monsma Jr, Y. Shen, H.Y. Meltzer and D.R. Sibley, 1994, Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors, J. Pharmacol. Exp. Ther. 268, 1403.

Sainati, S.M., J.W. Hubbard, E. Chi, K. Grasing and M. Brecher, 1995, Safety, tolerability and effect of food on the pharmacokinetics of iloperidone (HP 873), a potential atypical antipsychotic, J. Clin. Pharmacol. 35, 713.

Saller, C.F. and A.I. Salama, 1993, Seroquel: biochemical profile of a potential atypical antipsychotic, Psychopharmacology 112, 285.

Schwartz, J.-C., B. Giros, M.-P. Martres and P. Sokoloff, 1992, The dopamine receptor family: molecular biology and pharmacology, Semin. Neurosci. 4, 99.

Stockmeier, C.A., J.J. DiCarlo, Y. Zhang, P. Thompson and H.Y. Meltzer, 1993, Characterization of typical and atypical antipsychotic drugs based on in vivo occupancy of serotonin$_2$ and dopamine$_2$ receptors, J. Pharmacol. Exp. Ther. 266, 1374.

Strupczewski, J.T., K.J. Bordeau, Y. Chiang, E.J. Glamkowski, P.G. Conway, R. Corbett, H.B. Hartman, M.R. Szewczak, C.A. Wilmot and G. Helsley, 1995, 3-[[(Aryloxy)alkyl]piperidinyl]-1,2-benzisoxazoles as D_2 /5-HT_2 antagonists with potential atypical antipsychotic activity: antipsychotic profile of iloperidone (HP 873), J. Med. Chem. 38, 1119.

Szczepanik, A.M., L.R. Brougham, J.E. Roehr, P.G. Conway, D.B. Ellis and C.A. Wilmot, 1996, Ex vivo studies with iloperidone (HP 873), a novel atypical antipsychotic with D_2 /5-HT_2 receptor antagonist activity, J. Pharmacol. Exp. Ther. (in press).

Szewczak, M.R., R. Corbett, D.K. Rush, C.A. Wilmot, P.G. Conway, J.T. Strupczewski and M.L. Cornfeldt, 1995, The pharmacological profile of iloperidone, a novel atypical antipsychotic agent, J. Pharmacol. Exp. Ther. 274, 1404.

Tecott, L.H., L.M. Sun, S.F. Akana, A.M. Strack, D.H. Lowenstein, M.F. Dallman and D. Julius, 1995, Eating disorder and epilepsy in mice lacking 5-HT_{2c} serotonin receptors, Nature 374, 542.