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Short communication

Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile

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Abstract

Ziprasidone is a novel antipsychotic agent with a unique combination of pharmacological activities at human receptors. Ziprasidone has high affinity for human 5-HT receptors and for human dopamine D_2 receptors. Ziprasidone is a 5-HT_{1A} receptor agonist and an antagonist at 5-HT_{2A}, 5-HT_{2C} and 5-$HT_{1B/1D}$ receptors. Additionally, ziprasidone inhibits neuronal uptake of 5-HT and norepinephrine comparable to the antidepressant imipramine. This unique pharmacological profile of ziprasidone may be related to its clinical effectiveness as a treatment for the positive, negative and affective symptoms of schizophrenia with a low propensity for extrapyramidal side effects, cognitive deficits and weight gain. © 2001 Published by Elsevier Science B.V.

Keywords: Antipsychotic agent; Ziprasidone; Receptor binding, human

1. Introduction

Ziprasidone is a novel antipsychotic drug that is chemically distinct from other antipsychotic agents, with a unique combination of pharmacological activities. Ziprasidone has high affinity for 5-HT receptors including 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A} and 5-$HT_{1B/1D}$ as well as for dopamine D_2 receptors. In vitro and in vivo pharmacological studies (Seeger et al., 1995) suggest that ziprasidone may be effective in decreasing the positive and negative symptoms of schizophrenia, as well as treating symptoms of anxiety and depression that are often associated with schizophrenia. The receptor binding profile also predicts a low propensity for extrapyramidal side effects (Altar et al., 1986). Unlike other novel antipsychotic drugs, most of which can cause dramatic weight gain, ziprasidone is distinguished by its weight neutral profile (Allison et al., 1999), a clinical benefit that may derive from its unique pharmacology (Casey and Zorn, 2001). Results from efficacy and toleration studies with ziprasidone in patients with schizophrenia have been promising (Tandon et al., 1997; Daniel et al., 1999).

The present study extends the characterisation of ziprasidone's receptor pharmacology using nonhuman tissues (Seeger et al., 1995) to more relevant human receptors. Binding affinities for risperidone, olanzapine, quetiapine, clozapine and haloperidol are included for comparison.

2. Materials and methods

2.1. Drugs

Ziprasidone, olanzapine and quetiapine were synthesised at Pfizer Global Research and Development, Groton Laboratories (Groton, CT). Other drugs and reagents were purchased from Sigma (St. Louis, MO); radioligands were purchased from New England Nuclear (Boston, MA) or Amersham (Arlington Heights, IL).

2.2. Receptor binding and uptake studies

Radioligand binding and neurotransmitter uptake studies were performed as previously described (Seeger et al., 1995), with some modifications as indicated below. Human cortex, caudate and choroid plexus were obtained from the National Disease Research Interchange (Philadelphia, PA) or Rhode Island Hospital (Providence, RI). Cell lines expressing the human 5-HT_6 and 5-HT_7 recep-

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tors were obtained from Dr. David Sibley (NIH); those expressing the human muscarinic M_1 receptor were obtained from Dr. Thomas Bonner (NIH). Modifications of the procedures described by Seeger et al. (1995) included the use of [^{3}H]MK-912 ((2*S*,12*bS*,)1′,3′dimethylspiro(1, 2,4,5′,6,6′,7,12*b*-octahydro-2*H*-benzo(*b*)furo(2,3-a) quinazoline)-2,4′-pyrimidin-2′-one) (0.4 nM), [^{3}H]*N*-methylscopolamine (0.1 nM), [^{3}H]lysergic-acid (1.0 nM) and [^{3}H]5-carboxyamidotryptamine (0.3 nM) to label α_2-adrenoceptor, muscarinic M_1, 5-HT_6 and 5-HT_7 receptors, respectively. Incubations allowed for full association (data not shown) after which assay samples were filtered onto GF/B filters pre-soaked in 0.5% polyethylenimine. Nonspecific binding was determined using a saturating concentration of a known inhibitor for each of these receptors (Seeger et al., 1995). Radioactivity was quantified by liquid scintillation counting. Molar IC_{50} and molar apparent K_i values were calculated as described in Seeger et al. (1995) for receptor binding and uptake studies. Geometric means were calculated as the average of the molar pK_i values ± S.E.M.

2.3. Adenylate cyclase studies

Adenylate cyclase activity was measured in membranes derived from cells expressing the human 5-HT_{1A} receptor (from Dr. Marc Caron, Duke University, Durham, NC) as previously described (Seeger et al., 1995).

3. Results

3.1. Pharmacology of ziprasidone and comparative agents

Ziprasidone has very high, subnanomolar affinity for the human 5-HT_{2A} receptor and high affinity for the human dopamine D_2 receptor (Table 1). The affinity of ziprasidone for the human 5-HT_{2A} receptor is higher than those of olanzapine, quetiapine, clozapine and haloperidol, while its human dopamine D_2 receptor affinity is higher than those of olanzapine, quetiapine and clozapine but lower than that of haloperidol (Table 1). With the exception of quetiapine and haloperidol, all the compounds

Table 1
Affinities of antipsychotic agents for human receptors and rat transporters

Receptor	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Clozapine	Haloperidol
Dopamine D_1	6.88 ± 0.25 (3)	6.24 ± 0.03 (3)	7.28 ± 0.05 (3)	5.89 ± 0.05 (3)	6.54 ± 0.11 (3)	6.93 ± 0.08 (3)
	130 nM	580 nM	52 nM	1300 nM	290 nM	120 nM
Dopamine D_2	8.50 ± 0.12 (4)	8.67 ± 0.17 (4)	7.69 ± 0.11 (4)	6.75 ± 0.06 (3)	6.87 ± 0.10 (3)	8.87 ± 0.09 (3)
	3.1 nM	2.2 nM	20 nM	180 nM	130 nM	1.4 nM
Dopamine D_3	8.14 ± 0.03 (3)	8.02 ± 0.18 (3)	7.35 ± 0.12 (6)	6.50 ± 0.05 (3)	6.62 ± 0.05 (10)	8.61 ± 0.05 (3)
	7.2 nM	9.6 nM	45 nM	320 nM	240 nM	2.5 nM
Dopamine D_4	7.49 ± 0.11 (3)	8.07 ± 0.12 (3)	7.22 ± 0.21 (3)	5.65 ± 0.02 (6)	7.27 ± 0.06 (36)	8.48 ± 0.07 (3)
	32 nM	8.5 nM	60 nM	2200 nM	54 nM	3.3 nM
5-HT_{1A}	8.60 ± 0.08 (3)	6.68 ± 0.09 (3)	5.69 ± 0.09 (3)	6.64 ± 0.24 (3)	6.85 ± 0.09 (3)	5.44 ± 0.03 (3)
	2.5 nM	210 nM	2100 nM	230 nM	140 nM	3600 nM
5-$HT^a_{1B/1D}$	8.69 ± 0.04 (6)	6.76 ± 0.05 (5)	6.28 ± 0.01 (3)	< 5.29 (3)	5.77 ± 0.19 (3)	< 5.30 (3)
	2.0 nM	170 nM	530 nM	> 5100 nM	1700 nM	> 5000 nM
5-HT_{2A}	9.41 ± 0.05 (4)	9.54 ± 0.06 (4)	8.49 ± 0.16 (5)	6.66 ± 0.05 (3)	8.05 ± 0.03 (3)	6.91 ± 0.02 (3)
	0.39 nM	0.29 nM	3.3 nM	220 nM	8.9 nM	120 nM
5-HT_{2C}	9.14 ± 0.08 (8)	7.98 ± 0.08 (4)	7.99 ± 0.03 (4)	5.85 ± 0.02 (3)	7.76 ± 0.03 (5)	5.33 ± 0.04 (3)
	0.72 nM	10 nM	10 nM	1400 nM	17 nM	4700 nM
5-HT_6	7.12 ± 0.09 (3)	5.70 ± 0.01 (3)	7.99 ± 0.07 (3)	5.39 ± 0.11 (3)	7.98 ± 0.05 (3)	5.22 ± 0.04 (3)
	76 nM	2000 nM	10 nM	4100 nM	11 nM	6000 nM
5-HT_7	8.03 ± 0.13 (3)	8.52 ± 0.04 (3)	6.61 ± 0.23 (3)	5.75 ± 0.07 (3)	7.18 ± 0.05 (3)	5.95 ± 0.13 (3)
	9.3 nM	3.0 nM	250 nM	1800 nM	66 nM	1100 nM
α_1-Adrenoceptor	7.88 ± 0.12 (3)	8.86 ± 0.06 (3)	7.26 ± 0.05 (3)	7.83 ± 0.01 (3)	8.40 ± 0.07 (3)	8.33 ± 0.07 (3)
	13 nM	1.4 nM	54 nM	15 nM	4.0 nM	4.7 nM
α_2-Adrenoceptor	6.52 ± 0.01 (5)	8.30 ± 0.01 (3)	6.76 ± 0.05 (3)	6.00 ± 0.03 (3)	7.48 ± 0.02 (3)	5.92 ± 0.01 (3)
	310 nM	5.1 nM	170 nM	1000 nM	33 nM	1200 nM
Histamine H_1	7.33 ± 0.07 (3)	7.73 ± 0.09 (3)	8.56 ± 0.04 (3)	8.06 ± 0.11 (3)	8.74 ± 0.11 (3)	6.36 ± 0.09 (3)
	47 nM	19 nM	2.8 nM	8.7 nM	1.8 nM	440 nM
Muscarinic M_1	5.29 ± 0.10 (3)	5.55 ± 0.14 (4)	8.33 ± 0.16 (3)	6.99 ± 0.12 (4)	8.74 ± 0.04 (3)	5.80 ± 0.09 (4)
	5100 nM	2800 nM	4.7 nM	100 nM	1.8 nM	1600 nM
5-HT uptake[b]	7.27 ± 0.04 (7)	5.87 ± 0.06 (6)	< 4.83 (3)	< 4.70 (3)	5.41 ± 0.04 (3)	5.75 ± 0.03 (4)
	53 nM	1400 nM	> 15,000 nM	> 18,000 nM	3900 nM	1800 nM
Norepinephrine uptake[b]	7.31 ± 0.02 (6)	4.56 ± 0.06 (3)	5.71 ± 0.05 (3)	6.17 ± 0.05 (3)	6.41 ± 0.09 (3)	5.26 ± 0.06 (5)
	48 nM	28,000 nM	2000 nM	680 nM	390 nM	5500 nM

Data are presented as molar pK_i values ± S.E.M. (*n*).
[a] Bovine.
[b] Rat brain synaptosomes.

examined exhibit approximately 10-fold higher affinity for 5-HT_{2A} receptors than for dopamine D_2 receptors. Ziprasidone also has high affinity for human 5-HT_{2C}, 5-HT_{1A} and bovine 5-$HT_{1B/1D}$ receptors. The present data obtained from human receptors are consistent with previously reported data obtained from animal and human tissues (Seeger et al., 1995; Richelson and Souder, 2000). Risperidone, olanzapine and clozapine, like ziprasidone, have high affinity for the human 5-HT_{2C} receptor (Table 1), but only clozapine and olanzapine share ziprasidone's relative high affinity for 5-HT_{2C} receptors compared to their dopamine D_2 receptor affinity (Fig. 1A). The term relative affinity is used to refer to the drug's affinity for the indicated receptor relative to its dopamine D_2 receptor affinity. Quetiapine and clozapine have moderate affinity for human 5-HT_{1A} receptors (Table 1) but, like ziprasidone, have similar affinity for 5-HT_{1A} and dopamine D_2 receptors (Fig. 1A). Of the comparative agents tested, risperidone has moderate affinity for 5-$HT_{1B/1D}$ receptors, but only ziprasidone has similar high affinity for 5-$HT_{1B/1D}$ and dopamine D_2 receptors (Table 1; Fig. 1A).

Ziprasidone has moderate affinity for human α_1-adrenoceptor and histamine H_1 receptors and negligible affinity for human muscarinic M_1 receptors compared to its high dopamine D_2 receptor affinity as previously observed at nonhuman receptors. In contrast, quetiapine and clozapine have 10- and 32-fold greater affinity for α_1-adrenoceptors than for dopamine D_2 receptors (Fig. 1B). Compared with their dopamine D_2 receptor affinity, olanzapine, quetiapine and clozapine have high affinity for both histamine H_1 receptors (7-fold, 20-fold, and 70-fold greater, respectively; Fig. 1B) and muscarinic M_1 receptors (4-fold, 1.8-fold and 70-fold greater, respectively; Fig. 1B).

3.2. Inhibition of neuronal 5-HT and norepinephrine uptake

This study extends the results of a previous study by Seeger et al. (1995) in which it was demonstrated that ziprasidone inhibits both 5-HT and norepinephrine uptake into rat brain synaptosomes. Ziprasidone's affinity for these sites is similar to that of the antidepressants imipramine and amitriptyline (Fig. 1C), and is unique among the antipsychotics tested.

3.3. Functional evaluation of ziprasidone at human 5-HT_{1A} receptors

Adenylate cyclase studies using guinea pig hippocampal tissue have demonstrated that ziprasidone is a full agonist at 5-HT_{1A} receptors (Seeger et al., 1995). The present study evaluates ziprasidone's agonist activity at human 5-HT_{1A} receptors expressed in HeLa cells. In this preparation, ziprasidone was found to exhibit 5-HT_{1A} receptor agonist activity as evidenced by inhibition of forskolin-stimulated adenylate cyclase activity. Compared to the full agonist (*R*)-8-hydroxy-2-(di-*n*-propylamino)tetralin) [(*R*)-8-OH-DPAT], ziprasidone exhibits an average efficacy of $78 \pm 9\%$ and inhibits forskolin-stimulated adenylate cy-

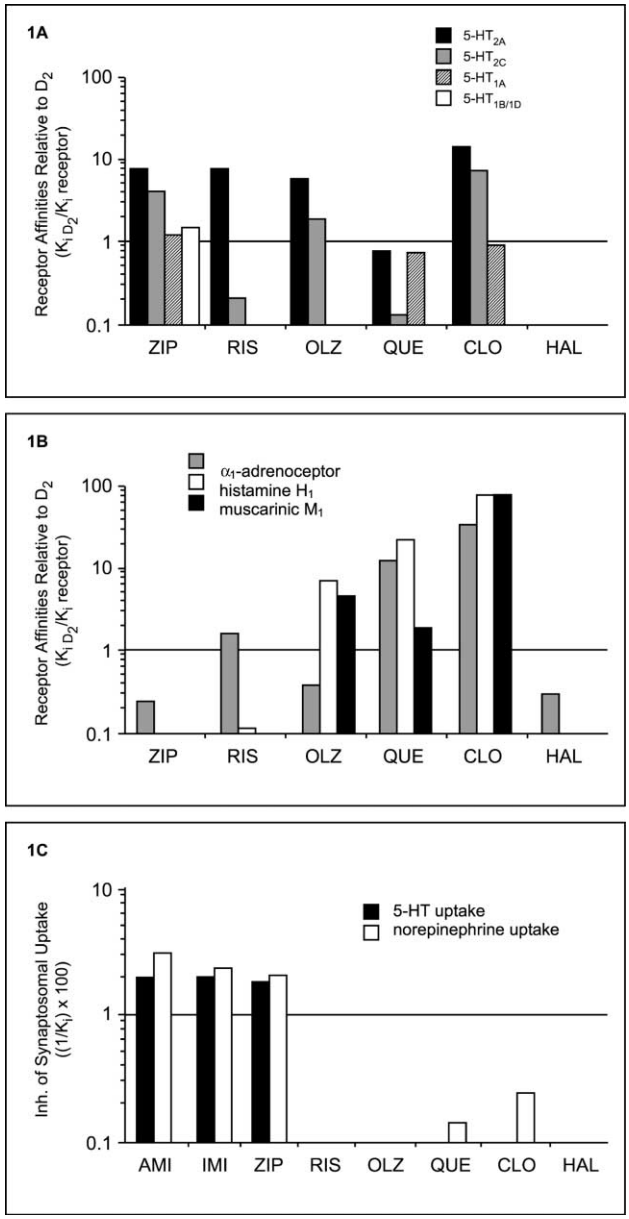

Fig. 1. (A) Ratio of affinities for human 5-HT_{2A}, 5-HT_{2C}, or 5-HT_{1A} and bovine 5-$HT_{1B/1D}$ receptors of ziprasidone (ZIP), risperidone (RIS), olanzapine (OLZ), quetiapine (QUE), clozapine (CLO) and haloperidol (HAL). Relative affinities (Table 1) are expressed as $K_{i\ D2}/K_{i\ receptor}$, where the bars above the line indicate higher affinity of each antipsychotic agent for the receptor indicated than for the dopamine D_2 receptor. (B) A comparison of affinities for human α_1-adrenoceptor, histamine H_1 and muscarinic M_1 receptors, relative to their dopamine D_2 receptor affinities. (C) Illustration showing that only ziprasidone inhibits uptake of 5-HT and norepinephrine in rat synaptosomes with similar affinity to amitriptyline (AMI) and imipramine (IMI). Affinities are expressed as $1/K_i$ value. Amitriptyline inhibits 5-HT and norepinephrine uptake with average pK_i values of 7.29 ± 0.10; 7.55 ± 0.13, respectively. Imipramine inhibits 5-HT and norepinephrine uptake with average pK_i values of 7.33 ± 0.04; 7.46 ± 0.10, respectively.

clase activity with an average pEC_{50} value of 7.44 ± 0.10 ($n = 5$). Inhibition of adenylate cyclase activity produced by 1 μM ziprasidone is blocked by 1 μM of *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl-cyclohexanecarboxamide (WAY-100635), a specific 5-HT_{1A} receptor antagonist.

4. Discussion

4.1. Human receptor binding profile of ziprasidone

An important differentiating feature of ziprasidone, in addition to its high affinity for 5-HT_{2A} receptors, is its high affinity for other 5-HT receptor subtypes, at which risperidone, olanzapine, quetiapine, clozapine and haloperidol bind with lower affinities or not at all. To date, all clinically efficacious antipsychotics have affinity for dopamine D_2 receptors. In fact, daily clinical dose and dopamine D_2 receptor occupancy are highly correlated with antipsychotic efficacy (Creese et al., 1976). The present study predicts that ziprasidone will occupy 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A} and 5-$HT_{1B/1D}$ receptors at doses needed to achieve whatever level of dopamine D_2 receptor occupancy is needed to result in clinical efficacy, given their similar receptor binding affinities. A comparison of the human receptor affinity profiles relative to their respective affinities at the human dopamine D_2 receptor show some striking differences between ziprasidone and the comparative agents used in this study (Fig. 1A,B). Ziprasidone has lower affinity for α_1-adrenoceptors compared to its dopamine D_2 receptor affinity in contrast to risperidone, clozapine and quetiapine (Fig. 1B). Both ziprasidone and risperidone have substantially reduced affinity for human histamine H_1 and muscarinic M_1 receptors compared with olanzapine, quetiapine and clozapine, which have several-fold higher affinities for histamine H_1 and muscarinic M_1 receptors than for dopamine D_2 receptors (Fig. 1B).

4.2. 5-HT_{1A} receptor agonist activity of ziprasidone

Ziprasidone has the highest affinity for human 5-HT_{1A} receptors among the antipsychotics tested, exceeding the affinity of clozapine by nearly two orders of magnitude. The agonist effect of ziprasidone at human 5-HT_{1A} receptors in adenylate cyclase studies extends previous findings of potent 5-HT_{1A} receptor-mediated agonist activity in guinea pig hippocampal membranes (Seeger et al., 1995). These results are in agreement with the in vitro findings of Newman-Tancredi et al. (1998), which show that ziprasidone acts as an agonist in ^{35}S-GTPγS binding studies using a human 5-HT_{1A} expressing cell line, although with somewhat lower intrinsic activity (55%). 5-HT_{1A} receptor agonist activity of ziprasidone has been confirmed in vivo, where the drug was observed to inhibit 5-HT_{1A} receptor-mediated firing in the dorsal raphe nucleus in a manner similar to 8-OH-DPAT (Sprouse et al., 1999) and to increase cortical dopamine release via 5-HT_{1A} receptor activation (Rollema et al., 2000).

4.3. Possible clinical attributes of ziprasidone

The unique pharmacological profile of ziprasidone may contribute to the beneficial clinical effects seen in patients while potentially offering advantages over other drugs. Ziprasidone has higher affinity for human 5-HT_{2A} receptors than for dopamine D_2 receptors. A high 5-HT_{2A}/dopamine D_2 receptor affinity ratio has been correlated with a lower propensity for extrapyramidal side effects and may also be advantageous for treating the negative symptoms of schizophrenia (Altar et al., 1986). In rodents, 5-HT_{1A} receptor agonist activity reduces motor side effects such as catalepsy induced by haloperidol (Wadenberg and Ahlenius, 1991). Clinically, 5-HT_{1A} receptor agonists such as buspirone have anxiolytic and antidepressant properties. Ziprasidone's 5-HT_{1A} receptor agonist, 5-HT/norepinephrine uptake inhibition and 5-$HT_{1B/1D}$ receptor antagonist activities (Seeger et al., 1995), either alone or in combination, predict efficacy for depressive and anxiety symptoms that are often associated with schizophrenia.

Ziprasidone's reduced affinity for human α_1-adrenoceptor versus dopamine D_2 receptors, suggests that it may have a lower potential to produce orthostatic hypotension and sedation in the clinic compared with drugs such as quetiapine, risperidone and clozapine, whose α_1-adrenoceptor antagonist affinity exceeds their dopamine D_2 receptor affinity. In contrast to clozapine, quetiapine and olanzapine, it is unlikely that ziprasidone will have anticholinergic side effects including cognitive dysfunction and gastrointestinal disturbances at doses relevant for antipsychotic efficacy.

4.4. Conclusions

In summary, ziprasidone's interaction with 5-HT receptors distinguishes it from all known clinically effective antipsychotic drugs. Specifically, ziprasidone is a potent 5-HT_{2A}, 5-HT_{2C} and 5-$HT_{1B/1D}$ receptor antagonist (Seeger et al., 1995) and a 5-HT_{1A} receptor agonist. Because ziprasidone's affinity for each of these receptors is similar to or greater than that for the dopamine D_2 receptor, significant interaction with these receptors will occur at doses required to achieve sufficient dopamine D_2 receptor blockade for antipsychotic efficacy. Of the antipsychotic agents tested in this study, only ziprasidone is a modestly potent inhibitor of 5-HT and norepinephrine uptake, with potency comparable to that of the antidepressant imipramine. Recent clinical studies have confirmed that ziprasidone is effective against positive, negative and depressive symptoms of schizophrenia, while showing a low propensity for extra-pyramidal side effects, cognitive deficits and weight gain (Tandon et al., 1997; Daniel et al., 1999).

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