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Binding of antidepressants to human brain receptors: focus on newer generation compounds

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Abstract. Using radioligand binding assays and postmortem normal human brain tissue, we obtained equilibrium dissociation constants (K_ds) for 17 antidepressants and two of their metabolites at histamine H_1, muscarinic, α_1-adrenergic, α_2-adrenergic, dopamine D_2, serotonin 5-HT_{1A}, and serotonin 5-HT_2 receptors. Several newer antidepressants were compared with older drugs. In addition, we studied some antimuscarinic, antiparkinson, antihistamine, and neuroleptic compounds at some of these receptors. For the antidepressants, classical tricyclic antidepressants were the most potent drugs at five of the seven receptors (all but α_2-adrenergic and 5-HT_{1A} receptors). The chlorophenylpiperazine derivative antidepressants (etoperidone, nefazodone, trazodone) were the most potent antidepressants at α_2-adrenergic and 5-HT_{1A} receptors. Of ten antihistamines tested, none was more potent than doxepin at histamine H_1 receptors. At muscarinic receptors antidepressants and antihistamines had a range of potencies, which were mostly weaker than those for antimuscarinics. From the in vitro data, we expect adinazolam, bupropion, fluoxetine, sertraline, tomoxetine, and venlafaxine not to block any of these five receptors in vivo. An antidepressant's potency for blocking a specific receptor is predictive of certain side effects and drug-drug interactions. These studies can provide guidelines for the clinician in the choice of antidepressant.

Key words: Histamine H_1 receptor – Muscarinic receptor – α_1-adrenoceptor, α_2-adrenoceptor – Dopamine D_2 receptor – Serotonin 5-HT_{1A} receptor – Serotonin 5-HT_2 receptor – Antihistamines – Antimuscarinics – Neuroleptics

Antidepressants are antagonists of many neurotransmitter receptors in human brain (Richelson and Nelson 1984a; Wander et al. 1986). The potency of this blockade can be used to predict the likelihood of adverse side effects and drug-drug interactions in clinical practice (Richelson 1993). Researchers can determine the potency of a drug for a specific receptor by obtaining the equilibrium dissociation constant (K_d) with a radioligand binding assay.

Since we last reported the results of this type of study, several new antidepressants have become available for use in the United States. Among those are sertraline and paroxetine (Fig. 1). Along with fluoxetine, these drugs have been classified as selective serotonin reuptake inhibitors (SSRIs), a term that refers to their selective inhibition of the neuronal re-uptake mechanism for serotonin compared to that for norepinephrine. Therefore, we wanted to find the binding potencies of these and some additional compounds at seven different receptors in human brain. We evaluated 17 antidepressants and two of their metabolites at the muscarinic, histamine H_1, α_1-adrenergic, α_2-adrenergic, dopamine D_2, serotonin 5-HT_{1A}, and serotonin 5-HT_2 receptors. Additionally, we examined a series of antimuscarinic, antiparkinson, antihistamine, and neuroleptic compounds at some of these receptors.

Methods and materials

Tissue preparation. Normal human brain tissue was obtained at the time of autopsy, on average 6 h after death, and stored in a liquid nitrogen refrigerator until it was homogenized in 10 vol of ice-cold 50 mM $NaKPO_4$ buffer, pH = 7.4, using a Brinkmann homogenizer, Model PT 10/30 (10 s, setting 6). The homogenate was spun at 38 000 *g* for 10 min in a Beckman model J2-21 centrifuge. The pellets were resuspended in fresh $NaKPO_4$ buffer and spun again at 38 000 *g*. The final pellets were resuspended in $NaKPO_4$, diluted to a concentration of 10 mg wet wt/ml and stored at −70°C until just before assay. For use in the radioligand binding assay, adequate amounts of tissue homogenates were thawed and spun as above. The pellets were resuspended in fresh $NaKPO_4$ buffer (pH = 7.4) in a volume that would provide the appropriate tissue weights in 0.1 ml aliquots (Table 1). For 5HT_{1A} assays the tissue homogenate of human cortex was processed further as described before (Peroutka 1986).

Radioligand binding assays. Assays were done on the Beckman Biomek 1000 workstation outfitted with a side arm loader (Cusack and Richelson 1993). Seven different receptors were studied using

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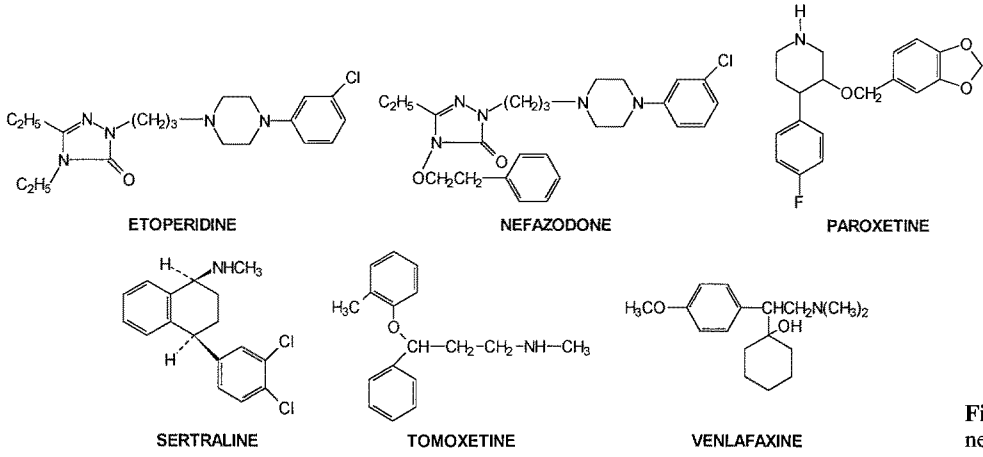

Fig. 1. Structures of some of the newer generation antidepressants

Table 1. Parameters used in radioligand binding assays[a]

Receptor	Radioligand		Estimation of non-specific bound		Human brain tissue used	
	[^{3}H]-Compound	~Final conc. (nM)	Compound	Final conc. (nM)	Brain region	Mg wet wt/tube
Muscarinic	QNB[b]	0.05	QNB	2.5	Caudate	0.7
Histamine H_1	Pyrilamine	1.0	Pyrilamine	250	Frontal cortex	10.0
α_1-Adrenergic	Prazosin	0.03	Prazosin	10	Frontal cortex	7.0
α_2-Adrenergic	Rauwolscine	0.4	Rauwolscine	25	Frontal cortex	10.0
Dopamine D_2	Spiperone	0.2	Spiperone	50	Caudate	1.5
Serotonin 5-HT_{1A}	8-OH-DPAT[c]	0.4	8-OH-DPAT	50	Frontal cortex	12.5
Serotonin 5-HT_2	Ketanserin	0.3	Ketanserin	25	Frontal cortex	2.5

[a] Incubation of assay mixture for the 5HT_{1A} receptor was at 25° C for 30 min. All other assay incubations were at 37° C for 60 min
[b] Quinuclidinyl benzilate
[c] 8-Hydroxy-2-(di-*n*-propylamino)tetralin

modifications of previously reported methods (Gozlan et al. 1983; Richelson and Nelson 1984a; Wander et al. 1987). Table 1 lists the radioligands and conditions for the different receptors. Incubation of assay mixture for the 5HT_{1A} receptor was at 25°C for 30 min. All other assay incubations were at 37°C for 60 min. After incubation the samples were rapidly filtered under vacuum using Whatman GF/B filters and a Brandel Cell Harvester. The tubes and filters were routinely rinsed with 5 × 1.5 ml ice-cold 0.9% NaCl. The filters were placed in minivials and 7 ml scintillation fluid was added. After the samples stood for 5 h, the radioactivity was measured using a Beckman LS5000 liquid scintillation counter. Specific binding to the receptor was calculated as the difference between the total binding (zero unlabeled ligand) and nonspecific binding (excess unlabeled ligand).

Data analysis. The data were analyzed using the LIGAND program (Munson and Rodbard 1980) to calculate equilibrium dissociation constants (K_d). The program has been modified by us to provide the Hill coefficient. Geometric mean of the K_d (Fleming et al. 1972) and its standard error (De Lean et al. 1982) were calculated. Unless noted otherwise, we present mean values from at least three independent experiments, each done in duplicate.

Source of materials. The radiochemicals [^{3}H]quinuclidinyl benzilate (QNB) (32.9 Ci/mmol), [^{3}H]pyrilamine (24.8 Ci/mmol), [^{3}H]prazosin (76.2 Ci/mmol), [^{3}H]rauwolscine (76.2 Ci/mmol), [^{3}H]8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) (164.5 Ci/mmol), [^{3}H]spiperone (21.6 Ci/mmol), and [^{3}H]ketanserin (60 Ci/mmol) were purchased from New England Nuclear (Boston, Mass., USA). The following compounds were generously provided by the manufacturers: adinazolam mesylate (Upjohn Co., Kalamazoo, Mich., USA); AF-DX 116 (Dr. Karl Thomae GmbH, Biberach Riss, Germany); amantadine HCl (Dupont Pharmaceuticals, Wilmington, Del., USA); astemizole, ketanserin tartrate (Janssen Pharmaceutica, Piscataway, N.J., USA); biperiden HCl (Knoll Pharmaceuticals, Whippany, N.J., USA); benztropine mesylate, cyproheptadine HCl (MSD, West Point, Pa., USA); bupropion HCl, procyclidine HCl, *d*-chlorpheniramine maleate, triprolidine HCl (Burroughs Wellcome Co., Research Triangle Park, N.C., USA); buspirone HCl, nefazodone (Bristol-Myers Squibb, Wallingford, Conn., USA); chlorprothixene (Hoffman La Roche, Nutley, N.J., USA); doxepin HCl, tomoxetine (Pfizer, Inc., Brooklyn, N.Y., USA); etoperidone HCl (Angelini Pharmaceuticals, Riveredge, N.J., USA): femoxetine HCl (Novo Nordisk, Måløv, Denmark); fluoxetine HCl, norfluoxetine maleate, and nortriptyline HCl (Eli Lilly and Co., Indianapolis, Ind., USA); fluvoxamine maleate (Duphar, Weesp, Netherlands); hydroxyzine di-HCl, sertraline HCl, desmethylsertraline maleate, prazosin HCl (Pfizer Central Research, Inc., Groton, Conn., USA); lofepramine HCl (Kabi Pharmacia Therapeutics, Helsingborg, Sweden); mequitazine (Pharmindustrie, Gennevilliers, France); paroxetine HCl (Smith Kline Beecham Pharmaceuticals, Surrey, UK); promethazine HCl, venlafaxine HCl (Wyeth-Ayerst,

Princeton, N.J., USA); terfenadine (Merrell Dow Pharmaceuticals, Cincinnati, Ohio, USA); and trazodone HCl (Mead Johnson Co., Evansville, Ind., USA). Melperone and bromperidol were gifts from Dr. R.J. Wyatt (NIMH, Washington D.C., USA). The following compounds were purchased: amitriptyline HCl, atropine sulfate, brompheniramine maleate, desipramine HCl, 5-hydroxytryptamine, creatinine sulfate complex, 8-hydroxy-2-(di-*n*-propylamino)-tetralin (8-hydroxy-DPAT) hydrobromide, orphenadrine HCl, pyrilamine maleate, and trihexyphenidyl HCl (Sigma Chemical Co., St Louis, Mo., USA); rauwolscine HCl (Indofine Chemical Co., Inc., Somerville, N.J., USA); and pimozide, quinuclidinyl benzilate (QNB), and spiperone (Research Biochemicals Inc., Natick, Mass., USA).

Results

The data for the equilibrium dissociation constants for antidepressants at seven different receptors are presented in Table 2. The compounds are presented alphabetically. Reference compounds are also presented at the bottom of this table. Hill coefficients for all compounds at all receptors were essentially equal to unity, showing that binding of these drugs obeyed the law of mass action.

Histamine H_1 receptor

We used [^{3}H]pyrilamine to study the histamine H_1 receptor of human brain frontal cortex. For pyrilamine (mepyramine) the K_d found in 19 independent experiments was 3.3 ± 0.2 nM. Figure 2A illustrates competition curves for some antidepressants at the histamine H_1 receptor in human brain. Among the antidepressants studied, doxepin and amitriptyline were very potent (Table 2). Adinazolam and venlafaxine were essentially inactive. The neuroleptic pimozide had a K_d of 24 ± 3 nM.

We also determined K_ds for several antihistamines, some of which were newer generation compounds. The compounds (geometric mean of $K_d \pm$ SEM) were astemizole (2.02 ± 0.05 nM), pyrilamine (3.3 ± 0.2 nM), brompheniramine (6.06 ± 0.09 nM), and terfenadine (9.7 ± 0.6 nM). None was more potent than the tricyclic antidepressants doxepin and amitriptyline.

Muscarinic receptor

For studying the muscarinic receptor, we used the human caudate nucleus and the radioligand [^{3}H]quinuclidinyl benzilate ($K_d = 28 \pm 1$ pM, $n = 11$). QNB is a nonselective muscarinic antagonist, having about equal affinity for the five subtypes of muscarinic receptors (Bolden et al. 1992). Representative competition curves are illustrated in Fig. 2B. Amitriptyline and doxepin were the most potent antidepressant antagonists, with K_ds = 9.6 and 23 nM, respectively (Table 2). Several compounds (adinazolam, bupropion, etoperidone, trazodone, and venlafaxine) were practically without activity. We also determined the binding potency of a series of antimuscarinic, antiparkinson, antihistamine, and neuroleptic compounds (Table 3). Pirenzepine has some selectivity for m_1 receptors (Buckley et al. 1989). AF-DX 116 has some selectivity for m_2 receptors (Buckley et al. 1989). In our studies with the five molecularly cloned muscarinic receptors (Stanton et al. 1993), we found no antidepressant selective for a given subtype of muscarinic receptor. Data for the neuroleptic chlorprothixene (Table 3) suggest that it is among the most potent for this class of compounds at blocking muscarinic receptors (Richelson and Nelson 1984b; Bolden et al. 1992).

α_1-Adrenoceptor

To study the α_1-adrenoceptor, we used the radioligand [^{3}H]prazosin, which had a $K_d = 0.11 \pm 0.01$ nM ($n = 11$). Prazosin appears to be nonselective for α_1-adrenoceptor subtypes (Morrow and Creese 1986). The antidepressants with the most potent binding at this receptor were doxepin and amitriptyline, which were equipotent (K_ds = 24 nM), and imipramine (Table 2). Representative competition curves are illustrated in Fig. 2C. Adinazolam and venlafaxine were the least potent competitive antagonists at this receptor and essentially inactive. Additionally, we tested the binding potency of the neuroleptic pimozide at this receptor and found a $K_d = 76 \pm 5$ nM.

α_2-Adrenoceptor

The radioligand, [^{3}H]rauwolscine, had a $K_d = 3.6 \pm 0.1$ nM, which was the most potent compound tested. Rauwolscine appears to be nonselective for α_2-adrenoceptor subtypes (Bylund et al. 1992). In addition, under the conditions of our assay, serotonin (up to 10 μM) and buspirone (up to 0.1 μM) had no effect on [^{3}H]-rauwolscine binding, contrary to the results of others (Convents et al. 1989).

This radioligand was competitively antagonized by antidepressants (for examples, see Fig. 2D). None of the antidepressants studied was very potent at the α_2-adrenoceptor (Table 2). Of the antidepressants studied, the most potent compounds were the structurally related chlorophenylpiperazine derivatives trazodone, etoperidone, and nefazodone. These were modestly potent, while adinazolam, bupropion, and venlafaxine were practically without activity.

$5HT_{1A}$ receptor

For this receptor the radioligand chosen was [^{3}H]8-hydroxy-DPAT. This compound was the most potent with a $K_d = 0.46 \pm 0.01$ nM. De Vos et al. (1991) suggested that rauwolscine is an agonist at this receptor. In our experiments rauwolscine had a $K_d = 7 \pm 1$ nM at this receptor, and therefore was not as potent as the agonists 8-hydroxy-DPAT, or 5-HT ($K_d = 0.72 \pm 0.03$ nM). [^{3}H]8-Hydroxy-DPAT was competitively antagonized by antidepressants (for examples, see Fig. 2E). Among the antidepressants tested, again the three chlorophenylpiperazines nefazodone, etoperidone, and trazodone were the most potent (Table 2). More than half the drugs evaluated were weak competitive antagonists in these radioligand binding studies.

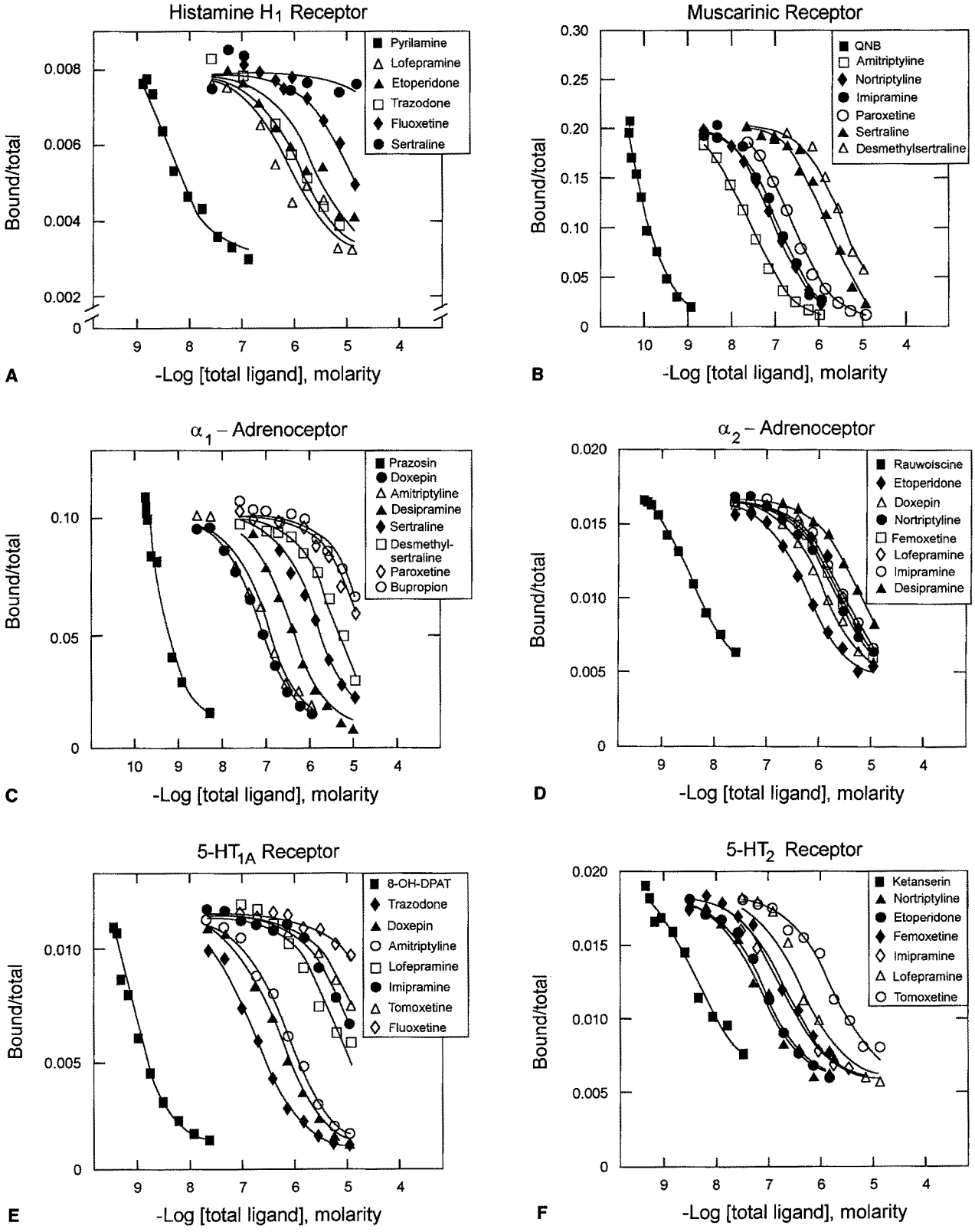

Fig. 2A–F

5HT$_2$ receptor

We used the antagonist [^{3}H]ketanserin to study the 5HT$_2$ receptor. It had a $K_d = 2.5 \pm 0.2$ nM ($n = 14$). [^{3}H]Ketanserin was competitively antagonized by antidepressants (for examples, see Fig. 2F). The classical tricyclic antidepressants and the chlorophenylpiperazine compounds had the highest K_ds (Table 2). Bupropion and venlafaxine were essentially without activity at this receptor.

Dopamine D$_2$ receptor

Using the human caudate nucleus, we found that [^{3}H]spiperone had a K_d of 0.18 ± 0.02 nM ($n = 21$), which

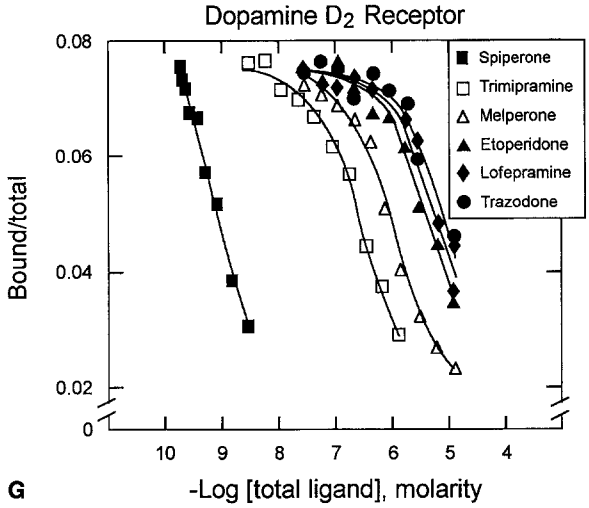

Fig. 2A–G. Competition between various antidepressants for binding sites in normal human brain tissue. Each graph presents the results of one representative experiment which was generated by computer with the use of the program LIGAND. The concentrations of unlabeled compounds were varied as indicated. The identities and concentrations of the radioligands used for each receptor are in Table 1

was nearly identical to our previously reported results (Richelson and Nelson 1984a). Spiperone was more potent than some other neuroleptics tested. These were bromperidol ($K_d = 3.7 \pm 0.1$ nM), pimozide ($K_d = 29 \pm 4$ nM), and melperone ($K_d = 620 \pm 30$ nM) had the highest affinity for the D_2 receptor. [^{3}H]Spiperone was competitively antagonized by antidepressants (for examples, see Fig. 2G). In comparison to all but the atypical neuroleptic melperone, all of the antidepressants studied were weak antagonists of the D_2 receptor. The most potent antidepressant was doxepin with a $K_d = 360 \pm 60$ nM, while the least potent were adinazolam, bupropion, tomoxetine, and venlafaxine (Table 2). Two additional antidepressants were tested only at this receptor. These were fluvoxamine with a $K_d = 770 \pm 60$ nM and trimipramine with a $K_d = 210 \pm 20$ nM. Trimipramine, which has an affinity for these receptors nearly as potent as that for the atypical neuroleptic clozapine (Richelson and Nelson 1984b), is also being considered as an atypical neuroleptic (Eikmeier et al. 1991).

Discussion

In this study we obtained data for a series of antidepressants and two of their metabolites at seven different receptor types in human brain tissue. These receptors included the histamine H_1, muscarinic acetylcholine, α_1- and α_2-adrenergic, dopamine D_2, and $5HT_{1A}$ and $5HT_2$ serotonergic receptors. We previously reported results for some of these antidepressants (Richelson and Nelson 1984a; Wander et al. 1986). Our results from the present study compare well with those from the earlier studies. The present study includes some newer, second generation compounds (Fig. 1), especially the SSRIs and some of their metabolites.

Among the SSRI metabolites, only fluoxetine and sertraline were available for us to test. The most potent of this group at blocking uptake of serotonin is paroxetine, while the most selective is sertraline (Bolden-Watson and Richelson 1993). Although the older compound trazodone is an SSRI, it is weaker than some non-SSRIs at blocking re-uptake of serotonin. In addition, it is much more potent at blocking serotonin receptors (Table 2 and Wander et al. 1986) than it is at blocking uptake of serotonin (Bolden-Watson and Richelson 1993). Thus, its net effect is to decrease serotoninergic neurotransmission (Fuller et al. 1984).

From our results presented here, we can make some generalizations when considering all the antidepressants as a group. First, their most potent receptor blocking effects were at the histamine H_1 receptor. Currently, of all classes of compounds, the most potent drugs available at blocking the human histamine H_1 receptor are the tricyclic antidepressants doxepin, amitriptyline, and trimipramine (cf. Table 2, Kanba and Richelson 1984; Richelson and Nelson 1984a,b). Second, the classical tricyclic antidepressants were the most potent compounds at blocking five of these seven receptors. The exceptions were at the α_2-adrenoceptor and the $5HT_{1A}$ receptor, where chlorophenylpiperazines were the most potent (Table 2). Third, most of the newer compounds were very weak at blocking neurotransmitter receptors. This last fact can explain why the newer compounds have significantly fewer of the side effects seen with the older compounds, especially the classical tricyclic antidepressants.

Venlafaxine was essentially without activity at all seven receptors (Table 2). However, from a practical standpoint, there were many other compounds that would not likely affect any of these seven receptors directly in vivo. These compounds included adinazolam, bupropion, fluoxetine, sertraline, and tomoxetine.

The new SSRI paroxetine was excluded from this list because of its relatively high potency at blocking muscarinic receptors. It was the most potent of the newer compounds at blocking this receptor, with an affinity close to that of imipramine (Table 2). These results are supported by our data from studies with the five cloned human muscarinic receptors (Stanton et al. 1993). In this study paroxetine was most potent at the m_3 receptor ($K_d = 80$ nM) and was four to eight fold less potent at the other four receptors. The m_3 receptor is highly expressed in glandular tissue. These data may explain the observation that paroxetine causes dry mouth in patients at an incidence, although low, significantly greater than does placebo (Smith and Glaudin 1992).

Molecular cloning studies have proven the existence of multiple subtypes of not only the muscarinic, but also the adrenergic and serotonin receptors. Well before we understand the functions of all these receptor subtypes, future research of the type reported by Stanton et al. (1993) will show whether antidepressants have selectivity for any of these subtypes.

Drugs that potently block certain receptors may cause particular adverse effects and potential drug-drug interactions in patients (Richelson 1993). For example, histamine H_1 receptor blockade may cause sedation and drowsiness and the potentiation of central depressant drugs. Muscarinic receptor blockade may cause blurred vision and memory dysfunction. Blockade of α_1-adrenoceptors may cause postural hypotension, while blockade

Table 2. Equilibrium dissociation constants for antidepressants at human brain receptors[a]

Antidepressants	Histamine H_1	Muscarinic	α_1-Adrenergic	α_2-Adrenergic	5 HT_{1A}	5 HT_2	Dopamine D_2
Adinazolam	>35000	>35000	>35000	>35000	>35000	17400 ±500	>35000
Amitriptyline	0.95±0.03	**9.6 ±0.3**	**24 ±2**	690 ±20	450 ±20	**18 ±1**	1460±90
Bupropion	11800 ±600	>35000	4200 ±300	>35000	>35000	>35000	>35000
Desipramine	60 ±1	66 ±2	100 ±10	5500 ±200	6400 ±300	350 ±20	3500±200
Desmethylsertraline[b]	9000 ±2000	1430 ±30	1200 ±100	7800 ±200	>35000	4800 ±300	11000±2000
Doxepin	**0.17±0.03**	23 ±2	23.5 ±0.9	1270 ±40	276 ±4	27 ±4	**360±60**[c]
Etoperidone	3100 ±400	>35000	38 ±1	570 ±10	85 ±2	36 ±3	2300±400
Femoxetine	4200 ±200	184 ±4	650 ±30	1970 ±60	2285 ±4	130 ±10	590±30
Fluoxetine	5400 ±500	590 ±70	3800 ±300	13900 ±200	32400 ±900	280 ±50	12000±1000
Imipramine	37 ±4	46 ±2	32 ±5	3100 ±100	5800 ±500	150 ±2	620±90
Lofepramine	360 ±40	67 ±1	100 ±3	2700 ±100	4600 ±200	200 ±40	2000±400
Nefazodone	24000 ±1000	11000 ±2000	48 ±2	640 ±30	**80 ±20**	26 ±2	910±40
Norfluoxetine[b]	11000 ±1000	810 ±40	3900 ±300	19000 ±700	13700 ±400	600 ±60	16000±1000
Nortriptyline	6.3 ±0.9	37 ±1	55 ±2	2030 ±30	294 ±4	41 ±4	2570±50
Paroxetine	22000 ±4000	108 ±5	4600 ±500	17000 ±400	>35000	19000 ±1000	32000±4000
Sertraline	24000 ±5000	630 ±30	380 ±50	4100 ±200	>35000	9900 ±1000	10700±800
Tomoxetine	5500 ±900	2060 ±50	3800 ±200	8800 ±100	10900 ±100	940 ±70	>35000
Trazodone	1100 ±200	>35000	42 ±3	**320 ±10**	96 ±5	25.0±0.7	3500±600
Venlafaxine	>35000	>35000	>35000	>35000	>35000	>35000	>35000
Reference compounds[d]							
Brompheniramine	6.06±0.09						
Atropine		1.96±0.03					
Prazosin			0.11±0.01				
Rauwolscine				3.6±0.1			
Serotonin					0.72±0.03		
Ketanserin						2.5±0.2	
Pimozide							29±4

[a] Values are geometric means±SEM in nanomolar. When SEMs are presented, compounds were tested in at least three independent experiments

[b] Metabolite of an antidepressant

[c] Trimipramine studied only at this receptor was more potent than doxepin with $K_d = 210 \pm 20$ nM

[d] These are not antidepressants. For the antidepressants the values in bold within boxes are the most potent for a given receptor

Table 3. Muscarinic receptor in human caudate nucleus: equilibrium dissociation constants

Compound	K_d, nM[a]
Antimuscarinics	
QNB	0.028 ± 0.001
Biperiden	1.2 ± 0.2
Trihexyphenidyl	1.4 ± 0.2
Benztropine	1.65 ± 0.02
Atropine	1.96 ± 0.03
Procyclidine	5.03 ± 0.06
Pirenzepine	8.5 ± 0.3
AF-DX 116	260 ± 20
Antihistaminics	
Mequitazine	3.2 ± 0.2
Cyproheptadine	5.9 ± 0.5
Promethazine	11 ± 1
Orphenadrine	43 ± 3
Diphenhydramine	310 ± 30
Triprolidine	400 ± 5
d-Chlorpheniramine	1300 ± 200
Terfenadine	1700 ± 100
Hydroxyzine	4600 ± 700
Pyrilamine	11000 ± 2000
Others	
Chlorprothixene[b]	16.0 ± 0.3
Pimozide[b]	800 ± 100
Buspirone[c]	16000 ± 1000
Amantadine[d]	40000 ± 10000

[a] Values are geometric means ± SEM. Compounds for which SEMs are presented were tested in at least three independent experiments
[b] This is a neuroleptic
[c] This is an anti-anxiety drug
[d] This is an antiparkinson drug

of α_2-adrenoceptors may antagonize the therapeutic effects of clonidine. Dopamine D_2 receptor blockade may cause extrapyramidal side effects such as parkinsonism and tardive dyskinesia. The clinical consequences of blockade of 5-HT_{1A} and 5-HT_2 receptors is much less certain than those for the other receptors.

These predictions are supported by the side effects found in a large multicenter study (Reimherr et al. 1991) for the classical tricyclic antidepressant amitriptyline, which potently blocks most of these receptors, compared to those for the SSRI sertraline, which would probably not affect these receptors. Therefore, clinicians can use these data to minimize or avoid certain adverse effects and drug-drug interactions in their patients.

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