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H1-Histamine Receptor Affinity Predicts Short-Term Weight Gain for Typical and Atypical Antipsychotic Drugs

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As a result of superior efficacy and overall tolerability, atypical antipsychotic drugs have become the treatment of choice for schizophrenia and related disorders, despite their side effects. Weight gain is a common and potentially serious complication of some antipsychotic drug therapy, and may be accompanied by hyperlipidemia, hypertension and hyperglycemia and, in some extreme cases, diabetic ketoacidosis. The molecular mechanism(s) responsible for antipsychotic drug-induced weight gain are unknown, but have been hypothesized to be because of interactions of antipsychotic drugs with several neurotransmitter receptors, including 5-HT_{2A} and 5-HT_{2C} serotonin receptors, H_1-histamine receptors, α_1- and α_2-adrenergic receptors, and m3-muscarinic receptors. To determine the receptor(s) likely to be responsible for antipsychotic-drug-induced weight gain, we screened 17 typical and atypical antipsychotic drugs for binding to 12 neurotransmitter receptors. H_1-histamine receptor affinities for this group of typical and atypical antipsychotic drugs were significantly correlated with weight gain (Spearman $\rho = -0.72$; $p < 0.01$), as were affinities for α_{1A} adrenergic ($\rho = -0.54$; $p < 0.05$), 5-HT_{2C} ($\rho = -0.49$; $p < 0.05$) and 5-HT_6 receptors ($\rho = -0.54$; $p < 0.05$), whereas eight other receptors' affinities were not. A principal components analysis showed that affinities at the H_1, α_{2A}, α_{2B}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_6 receptors were most highly correlated with the first principal component, and affinities for the D_2, 5-HT_{1A}, and 5-HT_7 receptors were most highly correlated with the second principal component. A discriminant functions analysis showed that affinities for the H_1 and α_{1A} receptors were most highly correlated with the discriminant function axis. The discriminant function analysis, as well as the affinity for the H_1-histamine receptor alone, correctly classified 15 of the 17 drugs into two groups; those that induce weight gain and those that do not. Because centrally acting H_1-histamine receptor antagonists are known to induce weight gain with chronic use, and because H_1-histamine receptor affinities are positively correlated with weight gain among typical and atypical antipsychotic drugs, it is recommended that the next generation of atypical antipsychotic drugs be screened to avoid H_1-histamine receptors.
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Keywords: atypical antipsychotic drugs; clozapine; weight gain; H_1-histamine receptors

INTRODUCTION

Atypical antipsychotic drugs, characterized by relatively high affinities for 5-HT_{2A} serotonin receptors and lower affinities for D_2-dopamine receptors (Meltzer *et al*, 1989), include clozapine, olanzapine, risperidone, quetiapine, and ziprasidone, and have been of considerable value in the treatment of schizophrenia (Meltzer, 1999a). The prototypical atypical antipsychotic drug clozapine has become the treatment of choice for treatment-resistant and treatment-intolerant schizophrenia and related disorders because of its greater efficacy (Kane *et al*, 1988; Meltzer *et al*, 1989) and lack of extrapyramidal sideeffects. Clozapine treatment also substantially decreases suicidality among patients with schizophrenia (Meltzer, 1999b; Meltzer and Okayli, 1995), and it may improve negative symptoms, cognition, and tardive dyskinesia. Other atypical antipsychotic drugs (eg olanzapine, risperidone, quetiapine, and ziprasidone) have also been reported to improve cognition, negative symptoms, and minimize the risks of tardive dyskinesia, when compared with typical antipsychotic drugs (Meltzer and McGurk, 1999; Meltzer *et al*, 1999).

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Atypical antipsychotic drugs may also have serious side effects, including sedation, orthostasis, constipation and, in the case of clozapine, a substantial risk of agranulocytosis. Several studies have now demonstrated that a number of typical and atypical antipsychotic drugs may induce both short- and long-term weight gain (Taylor and McAskill, 2000; McIntyre *et al*, 2001; Wetterling, 2001). Recently, the related side effects of hyperlipidemia, hyperglycemia, and hypertension have attracted considerable attention. In fact, a recent study (Fontaine *et al*, 2001) suggested that the magnitude of weight gain and its attendant increases in morbidity and mortality may greatly diminish the positive effects of those atypical antipsychotic drugs that produce these effects to the greatest extent, that is, olanzapine and clozapine.

The mechanism(s) responsible for antipsychotic-drug-induced weight gain are not understood. Altered glucose homeostasis and metabolism as well as increased food intake have been proposed as mechanisms responsible for antipsychotic-drug-induced weight gain. Typical and atypical antipsychotic drugs have a complex pharmacology, interacting with a number of serotonergic (eg 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 and 5-HT_7 (Roth *et al*, 1992, 1994, 1998), dopaminergic (eg D_2, D_3, and D_4 (Seeman and Lee, 1975; Seeman *et al*, 1997; Van Tol *et al*, 1991), histaminergic (eg H_1 (Peroutka *et al*, 1980) and H_4 (Nguyen *et al*, 2001)), adrenergic, and muscarinic acetylcholine receptors (Bolden *et al*, 1992; Zeng *et al*, 1997). In mice, targeted deletion of some of these receptors can have effects on body weight; for example, 5-HT_{2C} receptor knockout mice are obese (Tecott *et al*, 1995), whereas m3-muscarinic receptor knockout mice are lean (Yamada *et al*, 2001). The results with 5-HT_{2C} receptor and m3-muscarinic receptor knockout mice imply that the interactions of antipsychotic drugs with these receptors may be responsible for weight gain. Others have suggested that interactions of typical and atypical antipsychotic drugs with H_1-histamine receptors, or their relative affinities for the D_2 and 5-HT_{2A} receptors, may be responsible for antipsychotic-drug-induced weight gain (eg see Wetterling, 2001).

To determine which receptor(s) are most likely to be responsible for antipsychotic-drug-induced weight gain, we determined the affinities of 17 selected typical and atypical antipsychotic drugs for 12 human or rodent cloned receptors using the resources of the National Institute of Mental Health Psychoactive Drug Screening Program (NIMH-PDSP). We then attempted to correlate these receptor affinities with short-term weight gain data derived from a previous meta-analysis of the literature (Allison *et al*, 1999). The most robust predictor of a drug's propensity to induce weight gain was its affinity for the H_1 histamine receptor. Our findings predict that newer atypical antipsychotic drugs that have low H_1-histamine receptor affinities (eg ziprasidone, aripiprazole) will have low weight gain liabilities. These results also suggest that centrally active drugs with relatively higher H_1-histamine receptor affinities should be used with caution because of the propensity of these drugs to induce weight gain and the potential for subsequent hyperlipidemia, hypertension, and hyperglycemia.

METHODS

Materials

Typical and atypical antipsychotic drugs were obtained as previously described (Rauser *et al*, 2001), with the following exceptions: molindone was obtained from Research Diagnostics, Inc. (Flanders, NJ), whereas aripiprazole was a kind gift of Richard Mailman (University of North Carolina, Chapel Hill, NC). Cloned receptor preparations were obtained via the resources of the NIMH-PDSP as previously detailed (Rothman *et al*, 2000), with the exception of the human H_1-histamine receptor, which was cloned via PCR amplification of 'Quick-Clone' human cDNA (Clontech) and subcloned via NotI adaptors into the pUNIV-SIG expression vector (Kroeze Roth, unpublished vector sequence). The entire coding region was sequenced by automated dsDNA sequencing (Cleveland Genomics, Cleveland, OH) to verify that PCR-induced mutations had not occurred.

Radioligand Binding Assays

All binding assays were as previously described (Glennon *et al*, 2000; Rothman *et al*, 2000), primarily using cloned human receptor preparations. On-line protocols are available at http://pdsp.cwru.edu. Initial screening assays were performed at 10 μM concentration with quadruplicate determinations, and the percent inhibition of total specific binding was quantified. For drugs that caused $>50\%$ inhibition at 10 μM, full dose–response studies were performed using drug concentrations spanning 5–6 orders of magnitude. Typically, specific binding represented $>90\%$ of total binding. K_i values were calculated using GraphPad Prism (GraphPad Software, San Diego, CA, USA). All K_i values represent the mean of 3–4 separate determinations.

Statistical Analysis

Short-term weight gain data were derived from a meta-analysis of the literature (Allison *et al*, 1999). For all receptor–drug pairs, binding affinities (K_i's) in nanometers were converted to their log values; a maximum K_i of 10 000 nM ($\log K_i = 4.0$) was used for low-affinity interactions. All statistical analyses were carried out with the XLstat version 5.0 add-on package to Microsoft Excel from Addinsoft (Paris, France). For all analyses, *P*-values of less than 0.05 were considered significant.

RESULTS

Typical and Atypical Antipsychotic Drugs have a Complex Pharmacology

Initial screening assays were performed with a large number of typical and atypical antipsychotic drugs. In preliminary studies, we discovered that selected typical and atypical antipsychotic drugs interacted with virtually every biogenic amine receptor tested, in confirmation of many prior studies (see on-line database at http://pdsp.cwru.edu/pdsp.asp for comparison with published studies). We therefore narrowed our studies to a selected group of

biogenic amine receptors that have been most closely linked with weight gain or loss.

Comparison of Weight Gain with Selected Biogenic Amine Receptor Affinities

Since reliable weight gain data are available for only a subset of antipsychotic drugs (Allison *et al*, 1999), we more closely examined this set of drugs, which includes both typical and atypical antipsychotics. The typical antipsychotic drugs chosen for study were chlorpromazine, perphenazine, trifluoperazine, thioridazine, thiothixene, fluphenazine, haloperidol, molindone, and pimozide. The atypical antipsychotic drugs chosen were clozapine, olanzapine, loxapine, sertindole, risperidone, ziprasidone, quetiapine, and aripiprazole. Of importance for the present study, the typical antipsychotic drugs tested included those reported to induce substantial weight gain (chlorpromazine, perphenazine, thioridazine, thiothixene), those that induce little weight gain (fluphenazine, haloperidol), and those reported to induce weight loss (molindone, pimozide) in short-term studies (see Allison *et al*, 1999). Additionally, the atypical antipsychotic drugs included those that are reported to induce substantial weight gain in short-term studies (clozapine, olanzapine, quetiapine), those that induce moderate weight gain (risperidone), and those reported to induce minimal weight gain in short-term studies (ziprasidone, aripiprazole). We then examined the affinities of these receptors at a subset of 12 cloned biogenic amine receptors.

As can be seen graphically in Figure 1, and in Table 1, the tested drugs had a relatively complex pharmacology with substantial affinities for nearly all tested receptors. For the most part, high H_1-histamine receptor affinities were associated with drugs that cause weight gain, whereas drugs that induce little or no weight gain had low H_1-histamine receptor affinities. It is interesting to note that three atypical antipsychotic drugs that do not induce substantial short-term weight gain (ziprasidone, aripiprazole, risperidone) have relatively high affinities for 5-HT_{2C} serotonin receptors, in confirmation of recent studies showing that two of these drugs (risperidone, ziprasidone) are potent 5-HT_{2C} inverse agonists (Rauser *et al*, 2001). These results imply that neither 5-HT_{2C} receptor affinity nor 5-HT_{2C} receptor inverse agonist activity reliably predicts atypical antipsychotic drug-induced weight gain.

The Spearman correlation coefficients (a two-tailed nonparametric test was used, since the data deviate significantly from normality) of the relationship between the propensity of the drugs examined to induce weight gain and their affinities at the 12 receptors tested are given in Table 2. For 10 of 12 receptors, there was a negative relationship between K_i and weight gain; for the D_2 and 5-HT_7 receptors, there was a positive correlation between K_i values and weight gain. Only the correlations between weight gain and H_1, α_{1A}, 5-HT_{2C}, and 5-HT_6 receptor affinities were statistically significant.

It has been amply demonstrated that the ratio of an antipsychotic drug's affinity for the 5-HT_{2A} and the D_2 receptors is predictive of its atypicality (Meltzer *et al*, 1989). We therefore examined the relationship between the propensity of drugs to induce weight gain and the ratio of affinities for the various receptors tested and the affinity for the D_2 receptor (Table 3). When analyzed in this fashion, the affinities of eight of the 11 receptors examined were correlated to weight gain; however, the strongest relationship was again seen for the H_1, α_{1A}, and 5-HT_{2C} receptors.

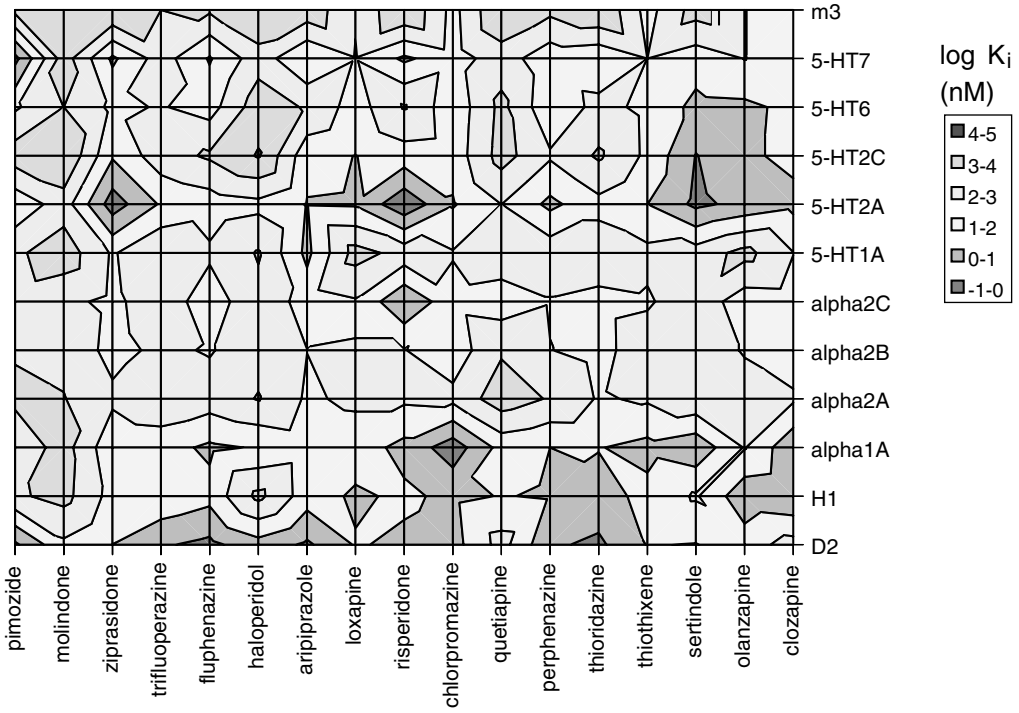

Figure 1 Surface plot of affinities of 17 typical and atypical antipsychotic drugs for 12 receptors. Drugs are in order of their propensity to induce weight gain, from the least on the left to the most on the right.

Table 1 Weight gain and binding data for typical and atypical antipsychotic drugs as used in this study

Drug	Class[a]	Weight gain (kg/10 weeks)[b]	K_i (nM)											
			5-HT_{2C}	5-HT_{2A}	D_2	H_1	M3	α_{1A}	α_{2A}	α_{2B}	α_{2C}	5-HT_{1A}	5-HT_6	5-HT_7
Aripiprazole	A	**0.71**	22.4	8.7	0.66	29.7	4677	26	74	102	37	5.57	783.2	9.6
Chlorpromazine	T	2.1	25	8	4	6	47	0.28	184	27	46	116.4	20.1	35.8
Clozapine	A	4	17	5.4	256	1.2	25	1.64	142	26	34	104.8	17	17.9
Fluphenazine	T	**0.43**	1386	30	0.54	21	1441	6.5	314.1	81.6	28.8	145.7	38	8
Haloperidol	T	**0.48**	10000	53	4	1800	10000	12	1130	480	550	1202	3666	377.2
Loxapine	A	**0.75**	9.5	7.7	12	7	122	31	150.8	107.6	79.9	2456	32.9	87.2
Molindone	T	**−1.06**	10000	320	63	2130	10000	2612	1097	557.8	172.6	3797	1008	3053
Olanzapine	A	3.51	6.8	2	34	2	105	115	314.1	81.6	28.8	2063	6.28	105.4
Perphenazine	T	2.79	132	5.6	1.4	8	1848	10	810.5	104.9	85.2	421	17	23
Pimozide	T	**−3.53**	3350	19	0.65	692	1955	197.7	1593	821.1	376.5	650	71	0.5
Quetiapine	A	2.61	2502	101	245	11	10000	22	3630	746.6	28.7	431.6	1865	307.2
Risperidone	A	1.67	35	0.17	6.5	15	10000	5	150.8	107.6	1.3	427.5	1188	6.6
Sertindole	A	2.94	0.9	0.58	9.1	130	2692	1.8	640	450	450	280	5.4	28
Thioridazine	T	2.81	60	10	11	19	43	5	134.3	341.3	74.8	180.7	57.1	99
Thiothixene	T	2.81	1400	50	0.63	4	10000	11	79.9	50.2	51.9	410.4	208.4	15.5
Trifluoperazine	T	**0.34**	378	13	1.3	63	1001	24	653.7	163.6	391.5	950	118	290.8
Ziprasidone	A	**0.28**	13	0.3	9.7	43	10000	18	160	48	59	76	60.9	6.62

[a]A, atypical; T, typical. [b]Data from Allison *et al* (1999, p 24) for later classification purposes, values in bold face were coded as 'no weight gain' and values in normal type were coded as 'weight gain'.

Table 2 Correlation between propensity of 17 drugs to induce weight gain and affinity ($\log K_i$) for 12 receptors

Receptor	Spearman correlation	
	ρ	*P*
D_2	0.361	NS
H_1	−0.723	<0.01
α_{1A}	−0.537	<0.05
α_{2A}	−0.370	NS
α_{2B}	−0.361	NS
α_{2C}	−0.323	NS
5-HT_{1A}	−0.208	NS
5-HT_{2A}	−0.373	NS
5-HT_{2C}	−0.493	<0.05
5-HT_6	−0.521	<0.05
5-HT_7	0.113	NS
m3	−0.408	NS

Table 3 Correlation between propensity of 17 drugs to induce weight gain and the ratio of the affinity for 11 receptors to the affinity for D_2 receptors

Receptor	Spearman correlation	
	ρ	*P*
H_1	−0.667	<0.01
α_{1A}	−0.611	<0.01
α_{2A}	−0.506	<0.05
α_{2B}	−0.465	<0.05
α_{2C}	−0.378	NS
5-HT_{1A}	−0.346	NS
5-HT_{2A}	−0.452	<0.05
5-HT_{2C}	−0.619	<0.01
5-HT_6	−0.548	<0.05
5-HT_7	0.228	NS
m3	−0.478	<0.05

Interestingly, no association was evident correlating weight gain with 5-HT_{2A}/D_2 affinity ratios, as has been recently suggested by others (eg Wetterling, 2001). In subsequent analyses, only the log K_i values, and not the ratio data, were used.

In order to examine the data more fully, a principal components analysis was performed (Table 4 and Figure 2). Initially, it was observed that there was a statistically significant relationship among many of the receptor affinities; this led to the computation of a correlation matrix based on the nonparametric Spearman correlation coefficient (Table 4). Because many of the variables studied were significantly correlated, a principal components analysis, which essentially 'uncorrelates' a set of correlated variables, was carried out. As can be seen in Figure 2, the 17 drugs studied could be segregated by this analysis into those that induce considerable weight gain and those that induce little or no weight gain. Drugs that induce weight gain tended to have low values on principal component 1, and high values on principal component 2. Principal component 1 explained 40% of the total variation in the data matrix, and principal component 2 explained an additional 18%. Principal components are composites of all the variables in a data matrix, and are mutually orthogonal in multi-dimensional space; the contributions of the variables to each principal component are weighted in such a fashion as to make them mutually orthogonal. The variables most closely correlated with principal component 1 were the affinities at the H_1, α_{2A}, α_{2B}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_6 receptors, and with principal component 2 they were weight gain and affinities for the D_2, 5-HT_{1A}, and 5-HT_7 receptors (data not shown).

The preceding analysis suggested that it might be possible to separate the drugs studied into two groups, those with a propensity to induce weight gain and those lacking this propensity, based on their affinities for particular receptors.

To further investigate this possibility, a discriminant functions analysis was carried out (Figure 3). This type of analysis maximizes the separation between two a priori groups, and determines which of the variables contribute most to this separation. This is then followed by an a posteriori reclassification of the groups to test whether the discriminant function can, in fact, adequately separate the two a priori groups. In order to exclude the trivial outcome that the weight gain data themselves would be the best predictor of the propensity to induce weight gain, weight gain data were excluded from this analysis. From Figure 3, it is clear that the drugs that induce weight gain can be discriminated from those that do not based only on receptor affinities. The variables most highly correlated to the discriminant axis were the affinities for the H1, and α_{1A} receptors (Table 5). In the a posteriori reclassification of the drugs, loxapine and fluphenazine, which do not induce weight gain, were classified with the group of drugs that does induce weight gain. Thus, 15 of 17 drugs (88.2%) were correctly classified by the discriminant functions analysis. We then attempted to classify the drugs by their affinities for individual receptors; only the H_1 receptor affinities correctly classified as many as 15 of the 17 drugs, with loxapine and sertindole being misclassified. For loxapine, this could be a reflection of how the weight gain data were extracted from the study of Allison *et al* (1999), or possibly

Table 4 Correlation matrix based on Spearman's nonparametric coefficient showing correlation between all pairs of variables examined

	Wt. gain	D_2	H_1	α_{1A}	α_{2A}	α_{2B}	α_{2C}	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	5-HT_6	5-HT_7	m3
Wt gain	1.00												
D_2	0.36	1.00											
H_1	**−0.72**	−0.23	1.00										
α_{1A}	**−0.54**	0.03	0.35	1.00									
α_{2A}	−0.37	0.06	**0.049**	0.34	1.00								
α_{2B}	−0.36	0.07	**0.67**	0.45	**0.66**	1.00							
α_{2C}	−0.32	−0.18	**0.63**	0.20	0.38	0.46	1.00						
5-HT1A	−0.21	0.23	0.21	**0.61**	**0.56**	**0.60**	0.33	1.00					
5-HT2A	−0.37	−0.19	0.34	0.37	0.40	0.47	0.21	0.34	1.00				
5-HT2C	**−0.49**	−0.31	0.43	0.26	**0.51**	**0.51**	0.22	0.34	**0.85**	1.00			
5-HT6	**−0.52**	−0.13	0.44	0.33	0.18	0.45	−0.03	0.23	**0.57**	**0.71**	1.00		
5-HT7	0.11	**0.49**	0.11	0.22	0.39	0.37	0.30	**0.57**	0.46	0.22	0.14	1.00	
m3	−0.41	−0.15	**0.48**	0.29	0.27	0.36	0.06	0.16	0.27	0.44	**0.71**	−0.06	1.00

Note that the first column recapitulates and data in Table 2. Significant values at the $P<0.05$ level (two-tailed test) are shown in bold face.

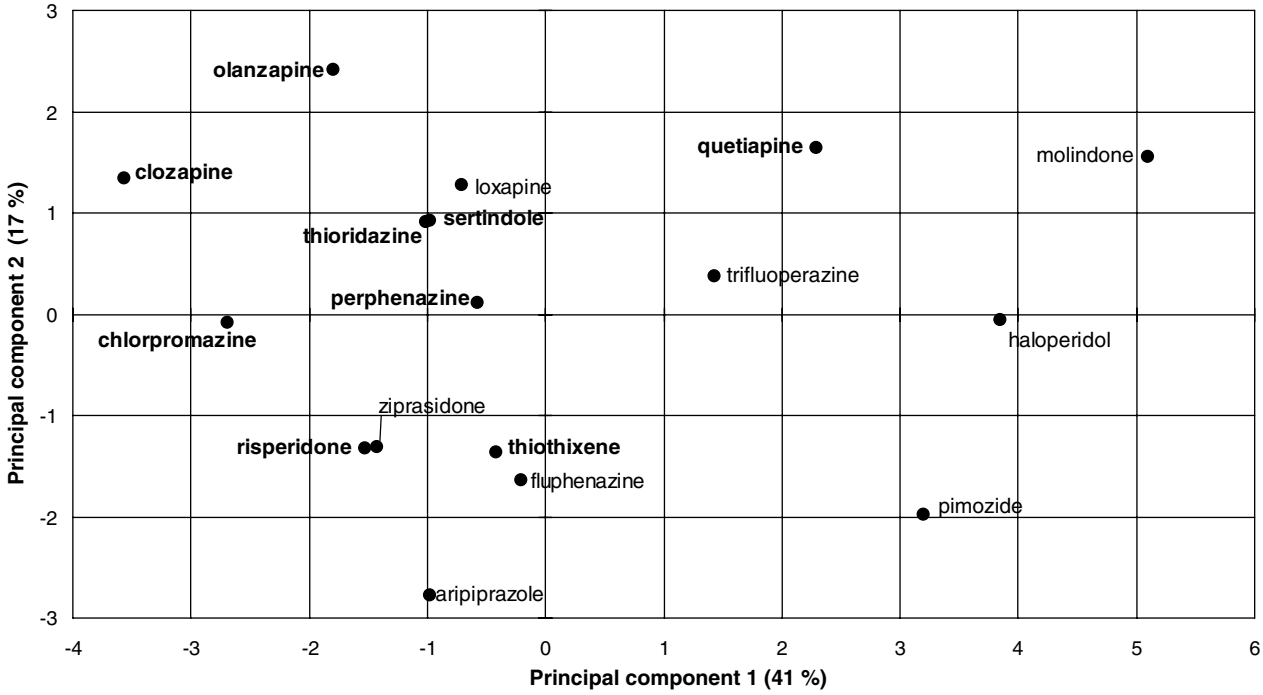

Figure 2 Principal components analysis of weight gain and receptor affinity data. Drugs that induce weight gain are shown in bold face. The horizontal axis is the first principal component, which explains 41% of the total variance in the data matrix, and the vertical axis is the second principal component, which explains 17% of the total variance in the data matrix.

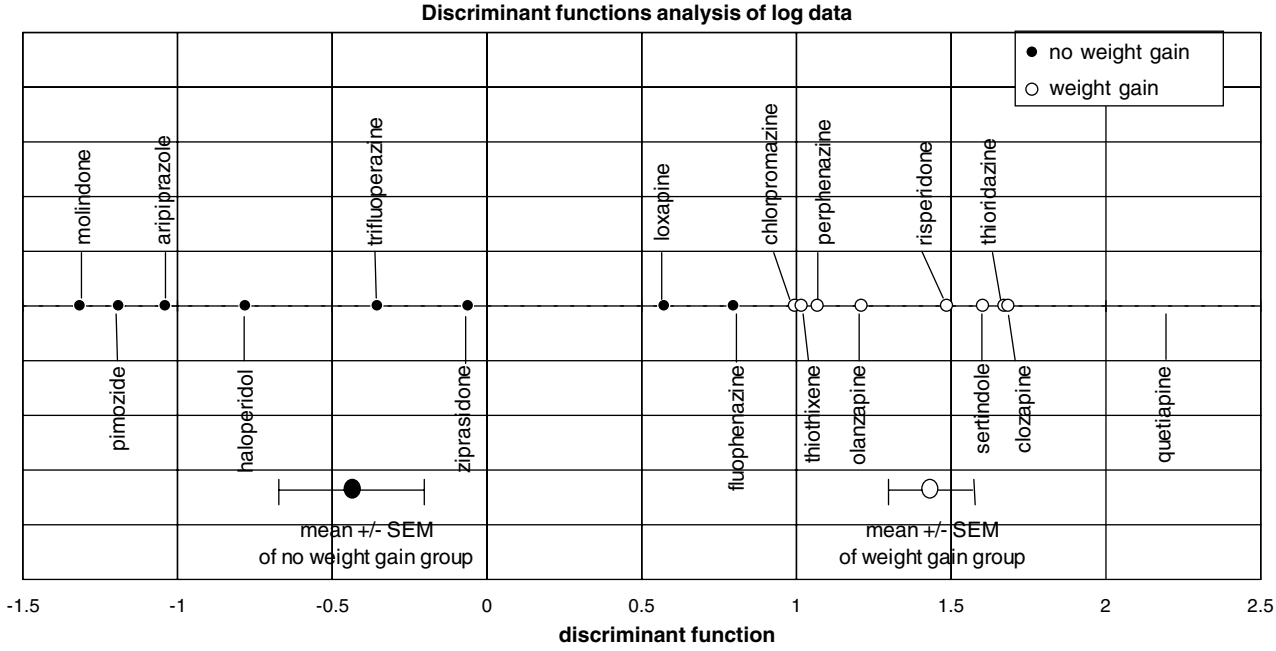

Figure 3 Discriminant function analysis of weight gain and receptor affinity data. The axis represents the discriminant function, which maximizes the separation between the two groups of drugs, those that do not induce weight gain (closed circles) and those that do induce weight gain (open circles). Weights of the variables that comprise the discriminant function are given in Table 5.

Table 5 Coordinates of the variables used for the discriminant functions analysis in Figure 3

Variable	Discriminant function coordinate
D_2	0.411
H_1	−0.726
α_{1A}	−0.609
α_{2A}	−0.146
α_{2B}	−0.262
α_{2C}	−0.487
5-HT_{1A}	−0.060
5-HT_{2A}	−0.325
5-HT_{2C}	−0.436
5-HT_6	−0.371
5-HT_7	−0.026
m3	−0.366

the relatively small sample size for loxapine in that study. Taken together, however, our analysis suggests that receptor binding affinities can predict a drug's propensity to induce weight gain, and that the affinity for the H_1-histamine receptor is the best single predictor of that propensity.

DISCUSSION

The major finding of this paper is that H_1-histamine receptor affinity is significantly correlated with short-term weight gain when a large number of typical and atypical antipsychotic drugs are examined. These results imply that antipsychotic drugs with relatively high H_1 receptor affinities are likely to induce short-term weight gain. These results also suggest that the next generation of atypical antipsychotic drugs should be screened for H_1-histamine receptor affinities and that drugs with relatively high H_1-histamine receptor affinities should be avoided. It has been known for several decades that (1) centrally active drugs with high affinities for H_1-histamine receptors can induce weight gain, (2) some antipsychotic drugs are potent H_1-histamine receptor antagonists, and (3) antipsychotic drugs can induce weight gain. Thus, it is perhaps not surprising that H_1-histamine receptor affinities predict weight gain for both selected typical and atypical antipsychotic drugs. What is surprising, however, is that H_1 receptor affinity was the only variable that reliably predicted weight gain for the typical and atypical antipsychotic drugs tested.

Several lines of evidence have suggested, in fact, that other receptors might be responsible for atypical antipsychotic-drug-induced weight gain, particularly the 5-HT_{2C} receptor. Thus, for instance, mice with targeted deletions of the 5-HT_{2C} receptor are obese (Tecott *et al*, 1995). Additionally, many typical and atypical antipsychotic drugs have high 5-HT_{2C} receptor affinities (Canton *et al*, 1990; Roth *et al*, 1992), and many antipsychotic drugs are potent 5-HT_{2C} inverse agonists (Herrick-Davis *et al*, 2000; Rauser *et al*, 2001). Finally, 5-HT_{2C} knockout mice are resistant to the anorectic effects of fenfluramine (Vickers *et al*, 1999), although chronic administration of potent and selective 5-HT_{2C} antagonists does not induce weight gain in rats (Wood *et al*, 2001). The present study clearly demonstrates that 5-HT_{2C} affinity does not predict weight gain among this group of typical and atypical antipsychotic drugs. However, this does not rule out the possibility that polymorphisms of the 5-HT_{2C} receptor (Lappalainen *et al*, 1995; Reynolds *et al*, 2002), or that altered expression of various editing isoforms of the 5-HT_{2C} receptor (Burns *et al*, 1997), might differentially contribute to variations in weight gain for individual subjects. Indeed a recent study (Reynolds *et al*,

2002) demonstrated that a polymorphism in the 5-HT_{2C} gene was highly associated with weight gain induced by either chlorpromazine or risperidone. Interestingly, both chlorpromazine and risperidone are rather weak inverse agonists at h5-HT_{2C}-INI receptors (Rauser *et al*, 2001), so it is unlikely that direct interaction of these drugs with 5-HT_{2C} receptors is important for the weight gain induced by both drugs. Instead it is more likely that the 5-HT_{2C} polymorphism predisposes individuals to weight gain via an unknown mechanism.

The mechanism(s) by which H_1-histamine antagonism might induce weight gain are currently unknown, although prior studies have amply demonstrated that H_1-histamine receptor antagonism increases feeding in rodents whereas H_2-histamine antagonism does not (Sakata *et al*, 1988; Fukagawa *et al*, 1989). Additionally, depletion of neuronal histamine increases feeding (Menon *et al*, 1971; Sakai *et al*, 1995). Interestingly, other psychoactive compounds with high H_1-histamine receptor affinities, for example, amitryptiline (Altamura *et al*, 1989), have been associated with significant weight gain. Finally, H_1-knockout mice are relatively resistant to the anorectic actions of leptin, and are prone to obesity when placed on high-fat diets (Masaki *et al*, 2001a, b). Taken together, these results imply that H_1-histamine receptors modulate feeding behavior via a leptin-dependent mechanism.

It is also clear that mechanisms other than H_1-histamine receptor blockade can also induce weight gain. Thus sulpiride, a selective D_2/D_3 antagonist, has virtually no affinity for H_1-histamine receptors (Roth *et al*, in preparation), yet it induces significant long-term weight gain among individuals with schizophrenia (Taylor and McAskill, 2000). Similarly, haloperidol and fluphenazine have relatively low H_1-histamine receptor affinities, yet, when given in depot formulations, have been reported to induce substantial weight gain (Taylor and McAskill, 2000). In this regard, it is interesting to note that the discriminant functions analysis predicts that fluphenazine will induce weight gain. Thus, factors independent of H_1-histamine receptor affinity may contribute to weight gain induced by typical and atypical antipsychotic drugs.

Taken together, these results clearly indicate that antipsychotic drugs with high H_1-histamine receptor affinities are associated with significant weight gain. These results are consistent with the evidence that two of the newer atypical antipsychotic drugs, ziprasidone and aripiprazole, are associated with less short-term weight gain. Finally, our results suggest that since the H_1-histamine receptor is the most likely molecular target responsible for atypical antipsychotic-drug-induced weight gain, high H_1-histamine receptor affinity should be avoided in the next generation of multireceptor atypical antipsychotic drug candidates.

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