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ORIGINAL PAPER

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Neuroendocrine responsivities of the pituitary dopamine system in male schizophrenic patients during treatment with clozapine, olanzapine, risperidone, sulpiride, or haloperidol

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Abstract *Background* Atypical antipsychotic drugs, in clinical doses, occupy 5-HT2 receptors near saturation, while D2 dopamine receptors, assessed usually in striatum by SPECT or PET methods, are occupied to different degrees. We hypothesized that these differences in D2 receptor occupancies may also be evaluated by a neuroendocrine approach, namely by measuring the plasma prolactin responses to i. m. administered haloperidol, since the expected elevations depend mainly on the free remaining D2 receptors in the tuberoinfundibular tract. *Methods* We measured the plasma prolactin levels at 0, 30, 60, 90, and 120 minutes after administration of 5 mg haloperidol i. m. in six groups of male patients with schizophrenia: a) 33 patients in a drug-free state, b) 15 patients on treatment with clozapine (range 200–600 mg/day), c) 15 patients on olanzapine (10–30 mg/day), d) 14 patients on risperidone (8–16 mg/day), e) 23 patients on haloperidol (10–40 mg/day), f) 14 patients on sulpiride (600–1600 mg/day). Data were also obtained from a group of 14 healthy male control subjects. The differences in baseline prolactin levels and in the responses to acute haloperidol of the seven groups were compared. *Results* The baseline prolactin levels did not differ significantly in the groups of controls (8.3±3.8 ng/ml), drug-free patients (8.0±3.6) and patients treated with clozapine (7.7±3.8), they were moderately elevated in patients treated with olanzapine (16.8±8.9), elevated in patients on haloperidol (34.4±17.3), and they were even higher in the groups of patients treated with risperidone (54.9±22.4) or sulpiride (58.8±27.0). All groups of patients gave attenuated prolactin responses to i. m. haloperidol compared to healthy controls. During treatment with haloperidol, risperidone, or sulpiride, no significant prolactin increases after i. m. haloperidol were observed. The group treated with olanzapine gave significant prolactin increases, which were lower than those obtained in the group of patients treated with clozapine, who gave responses similar to that of the drug-free patients. *Conclusions* Plasma prolactin levels and responses to i. m. haloperidol of patients on treatment with antipsychotic drugs, reflect the prolactin release potencies of the drugs, which are related, but not restricted, to their affinities to D2 dopamine receptors. According to the prolactin baseline levels and responses to i. m. haloperidol, the drugs of this study can be categorized for their potency to the pituitary dopamine system that controls prolactin release, as follows: sulpiride > risperidone > haloperidol > olanzapine > clozapine. This categorization is similar to that obtained by binding studies in striatal D2 dopamine receptors using brain imaging techniques.

Key words Schizophrenia · Prolactin · Haloperidol · Sulpiride · Clozapine · Olanzapine · Risperidone

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Introduction

A common feature of most atypical neuroleptics has been considered to be their stronger affinity to 5-HT2 serotonergic receptors than to D2 dopaminergic receptors [20]. Positron emission tomographic (PET) or single photon emission computed tomographic (SPECT) studies have revealed that in clinical doses, they occupy 5-HT receptors near saturation, even in low doses [10], while the occupation of D2 receptors can be very different, and varies as a function of dose. Typical neuroleptics, on the other hand, share four properties, namely they have an antipsychotic effect, induce extrapyramidal symptoms, have a cataleptic effect in animals, and cause substantial elevations of plasma prolactin. It is considered that typical neuroleptics, in order to induce an antipsychotic response, must occupy 70 % to 90 % of

the striatal D2 receptors [7, 21], and this degree of occupancy is related to extrapyramidal symptoms and plasma prolactin elevations.

Atypical neuroleptics, in certain cases, occupy D2 receptors at levels that would not be sufficient to induce an antipsychotic response [9]. Recent studies have shown dose-dependent D2 receptor occupancies during treatment with haloperidol of 67%–94% for doses of 5–20 mg/day [29], while clozapine occupies D2 receptors between 24% and 66% at doses of 75–900 mg/day [22], or 20%–49% for doses of 300–600 mg/day [29]. Olanzapine in doses 5–20 mg/day give 43–80% occupancy, in a dose-related manner [9]. Raedler et al. [25] found a mean of 50% occupancy at 5 mg/day, and 83% at 20 mg/day, Tauscher et al. [29] a mean of 75% occupancy at doses 10–25 mg/day, and Lavalaye et al. [13] a mean of 62% occupancy at 15 mg/day dose. Olanzapine thus shows higher D2 receptor occupancies than clozapine. Even higher, dose related, D2 receptor occupancies have been reported for risperidone, 63%–89% for 2–12 mg/day [9], 79%–85% for 6 mg/day and 53%–78% after reduction of the dose in 3 mg/day, and 70% mean occupancy at 4 mg/day [24]. Sulpiride, an antipsychotic drug which produces a lower incidence of extrapyramidal symptoms than typical neuroleptics [26], seems to behave like typical neuroleptics: a 78% occupancy of D2 dopamine receptors was found in the basal ganglia of a patient treated with 800 mg/day [6]. Sulpiride is highly potent in inducing elevations of plasma prolactin [1, 30].

The elevations of plasma prolactin (PRL) levels, induced by treatment of schizophrenic patients with these atypical neuroleptics, parallel the D2 receptor occupancies in the basal ganglia. Clozapine, the drug with lower D2 occupancy in therapeutic doses, does not, or moderately elevates PRL [19], while a switch from typical neuroleptics to clozapine reduces PRL levels to normal [16]. Olanzapine does not seem to elevate PRL at doses of 15 mg/day [13], but increased levels are found at higher doses [4, 9]. Risperidone causes substantial PRL elevations already at low doses [11, 13], and at clinically effective doses, PRL levels are even higher than those induced by haloperidol [17].

Neuroendocrine challenge tests offer another possibility for the investigation of receptor occupancies. For example, acute administration of haloperidol intramuscularly, increases plasma prolactin levels by occupying D2 receptors in the hypothalamus-pituitary, and the magnitude of the increases reflects the responsivity of the tuberoinfundibular dopamine pathway [8, 12, 14, 17]. The responses are attenuated if such receptors are occupied by a drug. In previous studies, we have shown that administration of 5 mg haloperidol i. m. causes within 2 hours significant PRL increases in drug-free schizophrenic patients, and these increases are attenuated after treatment with moderate neuroleptic doses, and abolished after treatment with high doses of haloperidol, or after treatment with risperidone in doses of 8–16 mg/day [14, 17].

In this study, we compare the prolactin responses to i. m. administered haloperidol in groups of male schizophrenic patients during treatment with haloperidol, sulpiride, clozapine, olanzapine, and risperidone, in doses administered for best clinical result, the responses of a group of drug-free patients, as well as those of a group of healthy male subjects. We hypothesized that the responses should be in line with the affinity of the drugs to D2 dopamine receptors. The tests in the treated patients were performed after a treatment period of six weeks. We also evaluated the differences in baseline prolactin levels among groups.

Patients and methods

All patients were hospitalized in the Athens University Psychiatric Clinic, Eginition Hospital. Informed consent was obtained from all subjects, and the study protocol was approved by the Ethics Committee of the hospital. Only male patients were included in the study, to avoid possible influences of variation in estradiol levels, known to affect dopaminergic receptor activity. Their ages ranged from 18 to 59 years, and the duration of illness from 1 to 26 years. The patients of the groups treated with atypical neuroleptics had been previously hospitalized, treated with typical neuroleptics, and in follow-up their therapeutic response was not considered to be satisfactory, so they were rehospitalized and switched to clozapine, olanzapine, or risperidone. A group of patients was tested in a drug-free period, after they had discontinued their medication. After hospitalization, they were kept neuroleptic-free for one week, and only benzodiazepines were administered when needed.

Six groups of patients were tested: a) 33 patients in a neuroleptic-free state, b) 23 patients on haloperidol, c) 14 patients on sulpiride, d) 15 patients on clozapine, e) 15 patients on olanzapine, and f) 14 patients on risperidone. The test was performed after the patients had been treated with a drug dose best for clinical response, for six weeks. Several patients are included in more than one group because they were tested twice, either in a drug-free state and later after treatment with one of the drugs, or during treatment with haloperidol and later, after switch to one of the atypical neuroleptics. For comparisons, we also tested a group of fourteen healthy male subjects. The age, duration of illness, score in the Brief Psychiatric Rating Scale, and drug doses, are shown in Table 1. It has to be mentioned that the relatively high BPRS score of the group of patients on haloperidol is due to the fact that it includes patients with no satisfactory therapeutic response to the drug, who were later switched to an atypical neuroleptic.

The haloperidol test was always performed between 8:00 and 9:00 hours by injecting 5 mg haloperidol intramuscularly. Blood samples for prolactin estimation were collected at times 0, 30, 60, 90, and 120 minutes. Plasma was separated by centrifugation, and stored at –30 °C until estimation, which was done in duplicate using commercially available radioimmunoassay kits (Serono, Italy). The inter- and intra-assay coefficients of variation were below 5%, and the concentrations of the hormone were expressed in ng/ml plasma.

For the statistical evaluation of the data, we used one-way analysis of variance with repeated measures (ANOVAR) separately for each group, followed by post hoc comparisons (Tukey test) to detect significant prolactin responses of the group. Two-way ANOVAR were also performed to compare the responses between groups. The non-parametric Spearman correlation coefficient test was used in determining correlations between baseline prolactin levels and maximal prolactin responses to clinical data, like age, duration of illness, and score in the BPRS.

Results

The clinical and neuroendocrine data of the seven groups of subjects studied are shown in Table 1, where

Table 1 Mean values ± SD of clinical data, baseline PRL (ng/ml), and maximal prolactin responses (DPRLmax, ng/ml) to acute haloperidol i. m. (maximal concentration in any of the four samples taken after haloperidol minus concentration at time zero) of the six groups of subjects studied. The relatively high BPRS score in the haloperidol group is due to the fact that it includes patients with no satisfactory therapeutic response to haloperidol, and who were later switched to an atypical neuroleptic. The number and percent of subjects with baseline PRL higher than the upper limit for normal males (15.9 ng/ml) are also given for each group

Group	N	Age	Range	Duration	Range	BPRS	Drug dose	Baseline PRL	PRL > 15.9 N	%	DPRLmax
Controls	14	31.7±10.6	21–50					8.3±3.8	1	7	45.5±18.9
Drug-free	33	32.2±9.2	18–59	10.3±7.6	1–26	56.1±13.7	–	8.0±3.6	3	9	33.0±16.4
Clozapine	15	32.9±7.9	24–47	13.1±7.0	3–26	31.8±6.5	310±102	7.7±3.8	1	7	29.9±18.3
Olanzapine	15	30.6±10.1	18–59	6.9±7.2	1–25	30.1±6.9	23.0±5.9	16.8±9.9	7	47	14.8±17.6
Haloperidol	23	28.7±5.0	20–38	8.1±4.3	1–17	48.8±5.8	19.0±8.9	34.4±17.3	22	96	4.4±10.0
Sulpiride	14	29.2±5.4	20–38	8.1±5.1	1–17	32.8±9.1	1214±298	58.8±27.0	14	100	–2.4±5.3
Risperidone	14	30.1±7.4	22–50	9.2±4.9	4–22	29.2±5.4	12.0±3.0	54.9±22.4	14	100	–1.8±2

the mean values and ranges are given for age, duration of illness, score in the BPRS, doses of the drugs, the baseline plasma prolactin levels (sample taken at time zero), and the maximal prolactin responses to i. m. haloperidol, calculated as the difference between the maximal prolactin level in the four samples taken after i. m. haloperidol administration, minus the level at time zero.

The individual baseline prolactin levels are shown in Fig. 1, and the maximal prolactin responses of the subjects to i. m. haloperidol in Fig. 2. There was a significant inverse correlation between the mean values of baseline prolactin and maximal prolactin responses of the six patient groups, which is shown in Fig. 3.

The ages of the subjects of the seven groups did not differ significantly. The duration of illness of the patient groups were similar (ANOVA, $F_{4,95} = 2.13$, $p=0.083$), with a non-significant tendency for shorter duration of illness of the groups of patients treated with olanzapine or haloperidol compared to the other groups. We tested if age and duration of illness were connected to the prolactin responses of each group, by relating them to the maximal prolactin response to i. m. haloperidol, using the non-parametric Spearman correlation coefficient test, and the correlations were all non-significant. The body weight of the subjects in the six groups were not different ($F=0.49$, $p=0.78$). This was tested, since in all subjects 5 mg haloperidol was administered for the haloperidol test, and the prolactin responses could be influenced by body weight. The mean values of the haloperidol administered i. m., in the six groups ranged from 0.059 to 0.063 mg/kg body weight, and did not differ significantly ($F_{6,121} = 0.44$, $p=0.85$).

The patterns of prolactin responses of the seven groups studied are presented in Fig. 4, and the results of the statistical evaluation in Table 2. All groups, except the group on haloperidol, gave significant changes of the prolactin levels after the administration of haloperi-

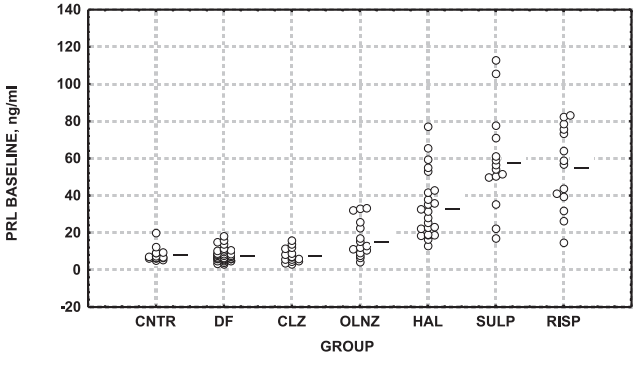

Fig. 1 Individual baseline prolactin levels of healthy control subjects, drug-free schizophrenic patients, and patients on treatment with clozapine, olanzapine, haloperidol, sulpiride, and risperidone. Mean values of the groups are also indicated.

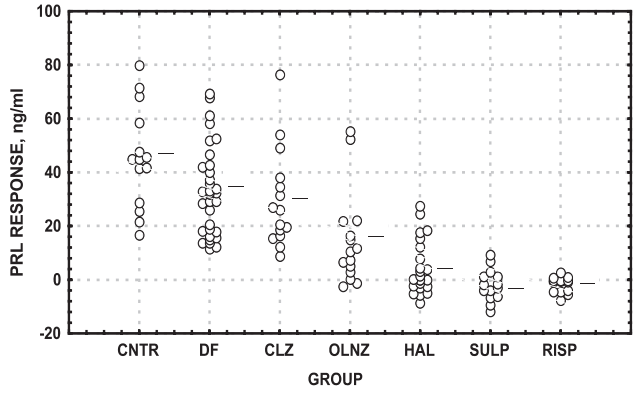

Fig. 2 Maximal prolactin responses to i.m. haloperidol of the subjects in the seven groups studied. The mean value of each group is also indicated.

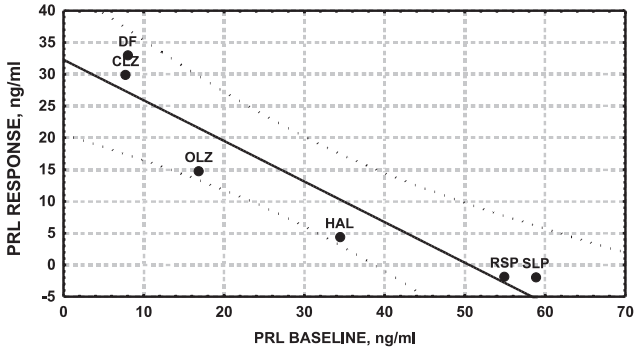

Fig. 3 Inverse correlation between the prolactin responses to i.m. haloperidol and the baseline prolactin levels of the six groups of schizophrenic patients (mean values), drug-free, and on treatment with clozapine, olanzapine, haloperidol, risperidone, and sulpiride.

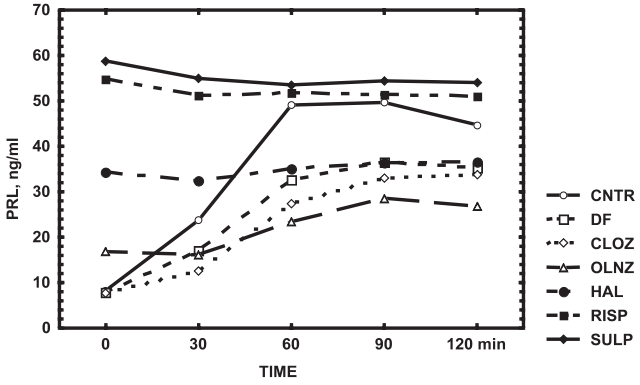

Fig. 4 Mean values of the prolactin responses to i.m. haloperidol of a group of healthy controls (14 subjects), drug-free schizophrenic patients (N=33), and groups of schizophrenic patients on six weeks treatment with clozapine (N=15), olanzapine (N=15), risperidone (N=14), and sulpiride (N=14).

dol. In the groups of control subjects, of drug-free patients, and of patients on clozapine and on olanzapine the prolactin plasma levels increased significantly after the administration of haloperidol i. m., while in the group of patients on sulpiride and on risperidone small but significant decreases were observed. The greatest increases were observed in the group of control subjects, followed by the group of drug-free patients, the group on clozapine, and the group on olanzapine. The mean values of these changes, as well as the baseline prolactin levels of the groups are shown in Table 1, and the statistical evaluation (ANOVA and post hoc comparisons) in Table 3.

Discussion

The baseline prolactin levels of the groups of drug-free patients after discontinuation of treatment with typical neuroleptics, and patients treated with clozapine, did not differ significantly from normal. This is in accordance with previous findings that a) after discontinuation of neuroleptics the elevated prolactin levels return to normal, and b) that during treatment with clozapine the prolactin levels are within the normal range [16, 19]. That clozapine does not elevate prolactin levels, can be attributed to its low D2 dopamine receptor occupancy, which has been found to be between 20 % and 49 % at doses of 300 to 600 mg/day for striatal D2 receptors [28], doses similar to those used in this study (200 to 600 mg/day). This, however, cannot be the only reason, since typical neuroleptics increase prolactin levels even in low doses, with D2 receptor occupancies similar to that of clozapine. An alternative or additional explanation could be that clozapine shows lower affinity towards the dopaminergic receptors of the tuberoinfundibular tract than those of the striatum.

During treatment with olanzapine, plasma prolactin levels were moderately elevated compared to controls, to drug-free patients, and to patients on clozapine, with the differences being close to significance (Table 3), and seven of the fifteen patients had levels over the upper limit for normals (47 %). This is in accordance with previous findings that olanzapine elevates plasma prolactin at higher doses only. Our patients received olanzapine doses from 10 to 30 mg/day (mean 23 ± 6), a relatively high dose, which is expected to elevate plasma prolactin (9).

The elevated plasma prolactin levels after treatment

Table 2 Statistical analysis of the prolactin response patterns after i. m. haloperidol in the six groups of subjects studied, as shown in Fig.4. One-way ANOVA for repeated measures was applied for each group. For the post hoc comparisons of the prolactin levels at times 30, 60, 90, and 120 minutes to baseline, the Tukey test was used

			Haloperidol-test			Post hoc comparisons, p <			
Group	N	Dose	df	F	p <	0′/30′	0′/60′	0′/90′	0′/120′
Controls	14		4,52	47.56	0.001	0.001	0.001	0.001	0.001
Drug-free	33		4,128	66.32	0.001	0.001	0.001	0.001	0.001
Clozapine	15	310±102	4,56	22.91	0.001	0.64	0.001	0.001	0.001
Olanzapine	15	23±6	4,56	5.87	0.005	0.99	0.28	0.007	0.028
Haloperidol	23	19±9	4,88	2.18	0.08	0.76	0.99	0.72	0.65
Sulpiride	14	1214±298	4,52	6.91	0.002	0.01	0.001	0.003	0.001
Risperidone	14	12±3	4,52	6.48	0.003	0.001	0.009	0.003	0.001

Table 3 Statistical evaluation of the differences in baseline prolactin levels and the maximal prolactin responses to i. m. haloperidol of the seven groups of subjects studied, mentioned in Table 1. In each column, the p value of the difference of the group from the reference group (Ref) is given

Group	Baseline prolactin ($F_{6,121}$=40.19, p < 0.001)						Maximal prolactin response ($F_{6,121}$=28.79, p < 0.001)					
Controls	Ref						Ref					
Drug-free	0.94	Ref					0.01	Ref				
Clozapine	0.91	0.95	Ref				0.004	0.49	Ref			
Olanzapine	0.11	0.05	0.08	Ref			0.001	0.001	0.005	Ref		
Haloperidol	0.001	0.001	0.001	0.003	Ref		0.001	0.001	0.001	0.03	Ref	
Sulpiride	0.001	0.001	0.001	0.001	0.001	Ref	0.001	0.001	0.001	0.001	0.90	Ref
Risperidone	0.001	0.001	0.001	0.001	0.001	0.47	0.001	0.001	0.001	0.001	0.20	0.16

with haloperidol, risperidone, and sulpiride are in accordance with several previous studies, and can be attributed to the high D2 receptor occupancies of these drugs as mentioned in the Introduction. The prolactin mean baseline levels under treatment with the five drugs of this study (Table 1) are related to their potency to occupy D2 receptors. Such a correlation of prolactin plasma levels to D2 receptor occupancy, measured in striatum by SPECT, has been reported by Schlegel et al. (28) for twelve male patients treated with haloperidol, benperidol, or clozapine. Similar results have been reported by Nordstrom and Farde (23), who found the plasma prolactin levels to correlate significantly with the D2 receptor occupancy in the putamen, measured by positron emission tomography, in thirteen schizophrenic patients treated with various doses of raclopride.

The group of drug-free patients showed significant prolactin increases after i. m. haloperidol (Fig. 4, mean maximal response 33.0±16.4 ng/ml), which were lower than the increases in the group of healthy subjects (mean response 45.5±18.9 ng/ml). This is in line with previous data that have shown, using neuroendocrine challenge tests, that discontinuation of neuroleptics leaves behind rather hyposensitive dopamine receptors (5, 15).

The prolactin responses to i. m. haloperidol reflect the responsivity of the pituitary dopamine system, which is influenced by the occupancy of D2 receptors by the antipsychotic drugs. Its responsivity after treatment with clozapine was found to be the same as in drug-free patients, presumably because the low degree of D2 receptor occupancy allows enough receptors free to be occupied by haloperidol, and to cause plasma prolactin elevations. It can also be assumed that clozapine binds loosely to hypothalamic D2 receptors, so that the drug can be easily replaced by haloperidol, which possesses higher binding affinity.

The responses under treatment with olanzapine were significantly attenuated. Under the doses used in this study (10–30, mean 23 mg/day), an occupancy of 60 to 80 % for striatal D2 receptors can be expected according to the reports mentioned in the Introduction. Similar occupancies for tuberoinfundibular D2 receptors, and a stronger binding capacity of olanzapine than clozapine, can well explain the attenuated prolactin responses to haloperidol.

Haloperidol treatment with doses of 10 to 40 mg/day (mean 18.9) as used in this study are expected to result in D2 receptor occupancies of more than 80 %, and the additional haloperidol administered i. m. will not change substantially the steady-state drug levels achieved after six weeks treatment.

An interesting finding of the study is the similar behavior of sulpiride and risperidone regarding their effects on prolactin release. Both drugs are known potent inducers of prolactin elevations, and this has been confirmed in the present study. The baseline prolactin levels of the patients treated with sulpiride or with risperidone were even higher than those of the patients treated with haloperidol. In addition, acute haloperidol administration caused small but significant reductions in plasma prolactin in the groups of patients treated with these two drugs. Sulpiride is known to produce a lower incidence of extrapyramidal symptoms than typical neuroleptics, and has been characterized as atypical [18, 27], although the drug is not known to block serotonin receptors to an appreciable extent [3].

The high baseline prolactin levels of the patients on sulpiride can be explained by the fact that sulpiride, because of its low lipid solubility, poorly penetrates the blood-brain barrier. Therefore, high levels of the drug need to be obtained outside the barrier by administering considerable amounts of the drug, in order to achieve an effect on dopamine receptors in the brain, and this results in a high occupancy of the pituitary dopamine receptors, which are outside the blood-brain barrier. A similar explanation may be valid for risperidone, which also has a high plasma to brain ratio, and which causes higher elevations of plasma prolactin than haloperidol, although it is a less potent D2 receptor antagonist, and a less potent prolactin releaser from pituitary cells in vitro (2).

Future assessment of D2 dopamine receptor occupancies in brain regions by SPECT or PET methods, and the evaluation of D2 receptor responsivity in the tuberoinfundibular tract by neuroendocrine methods in the same patients, may improve the understanding of the relations among receptor occupancy, plasma prolactin levels, and antipsychotic effect.

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