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The Differential Effects of Atypical Antipsychotics on Prolactin Elevation Are Explained by Their Differential Blood-Brain Disposition: A Pharmacological Analysis in Rats

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ABSTRACT

All atypical antipsychotics avoid extrapyramidal side-effects yet differ in their propensity to cause other side-effects, like prolactin elevation. We proposed that the atypical antipsychotics with a propensity for prolactin elevation would show a higher pituitary versus striatal D2 receptor occupancy. To investigate this hypothesis, we tested four atypical antipsychotics, two that are commonly associated with prolactin elevation (amisulpride and risperidone) and two that are less frequently associated (quetiapine and olanzapine). In particular, we calculated their ED_{50} values to increase plasma prolactin and block peripheral pituitary D2 receptors to their ED_{50} values to antagonize apomorphine-induced stereotypy and occupy central striatal D2 receptors. All antipsychotics dose dependently increased prolactin levels and antagonized apomorphine-induced stereotypy. However, the central to peripheral potency (ED_{50} for apomorphine antagonism to ED_{50} for prolactin elevation) differed remarkably across these drugs: amisulpride (21764), risperidone (14), quetiapine (10), and olanzapine (1.7). Compounds displaying a higher peripheral potency brought about higher prolactin levels for a given level of functional central antagonism. This dissociation between central and peripheral effects was explained by the differential occupancy of D2 receptors in the striatum versus in the pituitary [ratio of striatal/pituitary ED_{50} values (milligram per kilogram) for D2 occupancy): amisulpride (17/0.026 = 654), risperidone (0.89/0.081 = 14), quetiapine (24/4.1 = 6), olanzapine (0.30/0.43 = 0.7). These results indicate that dissociation between central and peripheral D2 receptor occupancy is a major determinant of the degree of prolactin elevation observed at therapeutic doses.

Atypical antipsychotics represent an important advance in the treatment of schizophrenia (Kapur and Remington, 2001). Although associated with significantly less extrapyramidal (Parkinson-like) motor side effects (EPS) (Geddes et al., 2000), the atypicals are not devoid of other side-effects. For example, some atypicals increase prolactin levels, whereas others are sedative, produce weight gain, or may induce diabetes in susceptible individuals (Stanniland and Taylor, 2000; Melkersson and Hulting, 2001). These differences in some areas are instructive in identifying important components of the mechanism of action. This is particularly the case with regard to antidopaminergic activity and endocrinological parameters. Although all the atypical antipsychotics have fewer EPS than typical antipsychotics, they differ among themselves in their prolactin-elevating effects (Kapur and Remington, 2001). Atypical antipsychotics such as risperidone (David et al., 2000) and amisulpride (Grunder et al., 1999; Stanniland and Taylor, 2000) are associated with a higher level of elevated prolactin than atypical antipsychotics such as olanzapine, clozapine, and quetiapine (Stanniland and Taylor, 2000). Thus, it seems that in this new class of atypical antipsychotics the motor and neuroendocrine side effects are dissociated.

At present, there is no satisfactory account of why some atypical antipsychotics elevate prolactin more than others. The most prominent theory of the action of atypical antipsychotics is the serotonin-dopamine theory (Meltzer et al., 1989). According to this account, a high ratio of affinity at the serotonin ($5\text{-}HT_2$) receptor to affinity at the dopamine D2 receptor is critical for atypical antipsychotic activity. This theory has focused on the explanation of motor side effects (Meltzer et al., 1989) and does not deal explicitly with prolactin elevation differences among the drugs. It is unlikely that a difference in the $5\text{-}HT_2$/D2 ratio would explain the prolactin differences because risperidone (a prolactin elevating drug) has a higher $5\text{-}HT_2$/D2 ratio than olanzapine and quetiapine (prolactin sparing drugs) (Schotte et al., 1996). Another proposed explanation of atypicality is based on a fast dissociation from the D2 receptor (Kapur and Seeman, 2001),

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ABBREVIATIONS: EPS, extrapyramidal symptoms; $5\text{-}HT_2$, serotonin.

but this account also does not deal specifically with prolactin elevation. Thus, clarifying the underlying mechanism for prolactin elevation by some atypical antipsychotics has both theoretical and practical importance.

Although both the motor side-effects and prolactin elevation have been related to D2 receptor blockade, different pathways are involved. The motor EPS of antipsychotics are associated with the blockade of postsynaptic D2 receptors in the striatum. This observation is now well established in both rodents and humans. In animals, it has been shown that catalepsy is related to striatal dopamine D2 receptor occupancy (Wadenberg et al., 2000), and in humans, it has been shown that EPS are observed only when more than 80% of the striatal D2 receptors are occupied (Kapur et al., 2000). On the other hand, prolactin elevation is associated with blockade of D2 receptors at the level of the anterior pituitary lactotrophs, where dopamine exerts a tonically inhibitory effect on prolactin secretion (Jaber et al., 1996). Although the D2 receptors (in terms of affinity and structure) are identical in both regions, the access of administered drugs to the two regions is very different. The anterior pituitary lies outside the blood-brain barrier and is accessible to drugs that do not cross the blood-brain barrier (Jaber et al., 1996). The functional importance of this difference is well exemplified by domperidone, a specific D2 blocker that does not cross the blood/brain barrier (Brown et al., 1981). Domperidone shows significant prolactin elevation in the absence of any central antipsychotic-like effects (Brown et al., 1981).

Based on the foregoing considerations, we proposed that a differential penetrability across the blood-brain barrier may account for the differential effects that the atypical antipsychotics have on prolactin elevation. To test this hypothesis, we first determined the peripheral effects on prolactin elevation for four chosen atypical antipsychotics, two that are associated with prolactin elevation (amisulpride and risperidone) and two that are less associated (olanzapine and quetiapine). Then, as an index of central effects, we examined their potency in blocking apomorphine-induced stereotypy. Finally, we related the differential potencies observed with these two methods to dopamine D2 receptor occupancies in the peripheral region, the pituitary, and the central region, the striatum.

Materials and Methods

Animals

Male Wiga Wistar rats (for testing apomorphine antagonism and D2 receptor occupancy) and female Sprague-Dawley rats (for evaluating prolactin release) were obtained from Charles River Breeding Facilities (Sulzfeld, Germany). The latter strain and sex were selected since it yielded very reproducible prolactin levels in pilot studies. The rats were housed in individual cages in air-conditioned laboratories (21 ± 2°C; 65 ± 15% relative humidity; 12-h light-dark cycle, lights on at 6.00 AM). They were fasted overnight, but tap water was made available ad libitum except during the test period.

Test Compounds

Risperidone and amisulpride were dissolved in distilled water containing two equivalents of tartaric acid, olanzapine in 10% hydroxypropyl-β-cyclodextrin containing two equivalents of tartaric acid, and quetiapine in distilled water containing 1% polysorbate 80. The solutions were stored at room temperature in closed containers protected from light and were administered by a single subcutaneous (s.c.) injection (10 ml/kg). Apomorphine antagonism was studied 0.5 h, and prolactin release and ex vivo receptor occupancy were studied 1 h after test compound administration. All doses were expressed in milligram base equivalents per kilogram body weight.

Tests

Prolactin Release in Rats. After an acclimatization period of at least 1 week, female Sprague–Dawley rats (180–220 g) were pretreated with test compound or solvent and decapitated 1 h later. Blood was collected in heparin-containing tubes and centrifuged at 3000 rpm for 10 min. Plasma was transferred into Eppendorf tubes and subsequently frozen. Samples were kept at <-18 °C until analysis. Plasma prolactin was measured with a commercially available radioimmunoassay Rat Prolactin ^{125}I assay system (Amersham Biosciences, Little Chalfont, Buckinghamshire, UK). The detection limit of the assay was 0.8 ng/ml. The interassay coefficient of variation was 7.2% at 7.7 ng/ml and 8.6% at 437 ng/ml.

Apomorphine Antagonism in Rats. Apomorphine-induced (0.90 mg/kg, i.v.) agitation (compulsive sniffing, licking, and chewing) was scored every 5 min for the 1st h after injection of apomorphine in male Wiga Wistar rats pretreated 30 min earlier with test compound or solvent. The score system was as follows: pronounced (3), moderate (2), slight (1), and absent (0). The criterion for drug-induced inhibition of agitation was a score of 3 less than seven times (0.8% false positives), a score of $\geq$2 less than seven times (0.3% false positives), or a score of $\geq$1 less than 7 times (0.3% false positives). The test is a slightly modified version of a procedure previously described in more detail (Brown et al., 1981).

Ex Vivo Autoradiography. Male Wiga Wistar rats (200 g) were decapitated 1 h after subcutaneous administration of vehicle or test compound (5–6 doses). Brains and pituitary glands were immediately removed from the skull and rapidly frozen in dry ice-cooled 2-methylbutane (−40°C). Twenty micrometer-thick sections were cut with a Leica CM 3050 cryostat-microtome (van Hopplynus; Brussels, Belgium) and thaw-mounted on microscope adhesive slides (Starfrost, Knittel, Germany). The sections were then kept at −20°C until use.

Occupancy of D2 receptors by drugs was measured both in the intermediate lobe of the pituitary gland and in the striatum, according to our standard protocol (Schotte et al., 1996). After thawing, sections were dried under a cold stream of air. The sections were not washed before incubation to avoid dissociation of the drug-receptor complex. Total binding was measured by incubating sections with 0.2 nM [^{125}I]iodosulpride (Amersham Biosciences) in a medium containing Tris-HCl buffer (50 mM, pH 7.4), 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, and 0.1% bovine serum albumin. Nonspecific binding was measured in the presence of 1 μM domperidone. Incubation was restricted to 10 min at room temperature to minimize dissociation of the drug from the receptor. To stop the incubation, the slides were washed (2 × 2 min) in Tris-HCl buffer, pH 7.4, at 4°C and then rapidly dipped in cold distilled water. Next the sections were dried under a stream of cold air, placed in a light-tight cassette, and covered with Ektascan GRL films (Eastman Kodak, Rochester, NY). After 1-week exposure, the films were developed in a Kodak X-Omat processor. Autoradiograms were quantified by means of an MCID image analyser (Imaging Research, St. Catharines, ON, Canada). Optical densities were transformed into levels of bound radioactivity after calibration of the image analyser with the aid of gray values generated by coexposure with the tissue sections of commercially available polymer standards (^{125}I Microascales; Amersham Biosciences). Specific binding was given as the difference between total binding and nonspecific binding measured in adjacent sections. Percentages of receptor occupancy by the drug administered to the animal correspond to 100% minus the percentage of receptor labeling in the treated animal.

General Procedure and Statistics

All experiments were performed by unbiased, trained technicians who used coded solutions. Doses were selected from the geometrical series 0.00063, 0.00125, 0.0025. . . 40, 80, 160 mg/kg in such a way that at least three doses covered the dose-response curve. Each dose group consisted of five animals for the functional studies and three to five animals per dose for the receptor occupancy studies. Control injections of solvent were included in each experimental session. For the functional studies, all-or-none criteria for significant ($p < 0.05$) effects were defined by analyzing a frequency distribution of a large series of historical control data. On the basis of the criteria obtained in this way, ED_{50} values (the dose inducing a biologically significant change in 50% of the animals) and corresponding 95% confidence limits were determined according to the modified Spearman-Kaerber estimate using theoretical probabilities instead of empirical ones (Tsutakawa, 1982). The modification entails using a linearized log dose-response curve to tabulate the ED_{50} and its confidence interval as a function of the slope and yields almost identical estimates ($r = 0.99$) of ED_{50} compared with the maximum likelihood method (Finney, 1962) with smaller and meaningful confidence intervals. Details on the modification and its validation are available upon request (Lewi et al., 1977).

For the ex vivo autoradiographic studies, the percentage of receptor occupancy was plotted against the dose, and a best-fit sigmoidal log dose-occupancy curve was calculated by nonlinear regression analysis with the GraphPad Prism program (GraphPad Software, San Diego, CA). From these best-fit dose-occupancy curves, the ED_{50} values (the dose producing 50% receptor occupancy) were obtained with 95% confidence limits were calculated. The program also yields two other values describing how well the data conform to the sigmoidal log dose-occupancy relationship; the r^2 value indicates the percentage of variance in occupancy that is explained as a sigmoidal function of log dose and a p value, which is obtained using a nonparametric "runs test" that tests whether the data points systematically deviate from the sigmoidal curve. It is important to note that using the runs test a p value <0.05 suggest that the data do systematically differ from the curve, whereas p values >0.05 and closer to unity suggests that the data do not systematically differ from the theoretical curve.

Results

Prolactin Release. As local irritation may induce stress and thereby increase prolactin, it is important to note that no differences between the various solvent groups were observed. In solvent-pretreated control rats, the average prolactin level was 3.5 ± 0.7 ng/ml (mean ± S.E.M.; $n = 77$), ranging from 0.8 to 32 ng/ml. One control displaying an exceptional high prolactin level of 1050 ng/ml was discarded. Values below the detection limit of 0.80 ng/ml were set at 0.80 ng/ml for calculating mean values. Only 4 of these 77 rats displayed a level above 20 ng/ml. Therefore, prolactin concentrations above 20 ng/ml were considered to reflect a significant increase in prolactin levels in rats pretreated with test compound.

Table 1 lists plasma prolactin concentrations measured 1 h after subcutaneous injection of vehicle or the indicated doses of the test compounds. Table 2 lists the ED_{50} values of the test compounds for increasing prolactin to above a level of 20 ng/ml—the level deemed to be a significant elevation. The test compounds dose dependently increased prolactin levels. The dose of the drug, in terms of ED_{50}, to elevate prolactin levels beyond 20 mg/kg was amisulpride (0.0017 mg/kg), risperidone (0.0050 mg/kg), olanzapine (0.10 mg/kg), and quetiapine (0.55 mg/kg). The prolactin levels increased progressively with dose increases up to a certain maximum level (approximately 500 ng/ml; not reached with all compounds within the tested dose range).

Antagonism of Apomorphine-Induced Abnormal Behavior. Table 2 lists the ED_{50} values of the test compounds for antagonism of apomorphine-induced stereotypy. In terms of ED_{50}, the potency order was risperidone (0.070 mg/kg), olanzapine (0.10 mg/kg), quetiapine (5.8 mg/kg), and amisulpride (37 mg/kg).

Dissociation between Prolactin Release and Apomorphine Antagonism. Table 2 compares the ED_{50} for

TABLE 1

Plasma prolactin levels (nanograms per milliliter; mean ± S.E.M.) measured 1 h after s.c. injection of solvent or the indicated doses of the compounds

The last column lists the fraction of rats displaying prolactin levels > 20 ng/ml (adopted as all-or-none criterion for significant prolactin release).

Test Compound	Dose	N_{tested}	Prolactin[a]	$N_{>20\ ng/ml}/N_{tested}$
	mg/kg, s.c.		*ng/ml; mean ± S.E.M.*	
Solvent	0	77[b]	3.5 ± 0.7	4/77
Amisulpride	0.00063	5	12 ± 3	1/5
	0.0025	5	22 ± 7	3/5
	0.01	5	115 ± 49	5/5
	0.04	3	505 ± 177	3/3
	0.63	3	464 ± 55	3/3
	2.5	3	464 ± 48	3/3
	10.0	3	504 ± 142	3/3
Risperidone	0.0025	5	6.6 ± 3.2	0/5
	0.01	5	50 ± 7	5/5
	0.04	5	469 ± 149	5/5
	0.16	5	560 ± 132	5/5
Olanzapine	0.04	5	2.9 ± 1.2	0/5
	0.16	5	76 ± 32	4/5
	0.63	5	118 ± 29	5/5
	2.5	5	388 ± 103	5/5
Quetiapine	0.16	5	11 ± 3	0/5
	0.63	5	28 ± 14	3/5
	2.5	5	130 ± 21	5/5
	10.0	5	410 ± 109	5/5

[a] Values below the detection limit of 0.80 ng/ml were set at 0.80 ng/ml for the purpose of calculating mean values.
[b] Exclusive of one control rat displaying an exceptional high value of 1050 ng/ml.

TABLE 2

ED_{50} values (95% confidence limits; milligrams per kilogram, s.c.) of four currently available antipsychotics for the induction of prolactin release, the antagonism of apomorphine-induced abnormal behaviour, and the occupancy of D2 receptors in the pituitary and the striatum

Compound	ED_{50} for Elevating Prolactin > 20 ng/ml			ED_{50} for D2 Receptor		
	Prolactin Release	Apomorphine Antagonism	Ratio	Pituitary	Striatum	Ratio
	mg/kg, s.c.; 95% CL[a]			*mg/kg, s.c.; 95% CL*[b]		
Amisulpride	0.0017 (0.00074–0.0037)	37 (28–51)	21764	0.026 (0.017–0.038) [r^2: 0.90; p: 0.12]	17 (15–19) [r^2: 0.98; p: 0.76]	654
Risperidone	0.0050 (0.0032–0.0077)	0.070 (0.047–0.102)	14	0.081 (0.053–0.122) [r^2: 0.90; p: 0.14]	0.89 (0.68–1.17) [r^2: 0.96; p: 0.94]	11
Quetiapine	0.55 (0.30–1.00)	5.8 (4.6–7.1)	10	4.1 (2.4–7.1) [r^2: 0.84; p: 0.063]	24 (14–40) [r^2: 0.88; p: 0.063]	6
Olanzapine	0.10 (0.058–0.19)	0.17 (0.12–0.23)	1.7	0.43 (0.37–0.49) [r^2: 0.98; p: 0.75]	0.30 (0.26–0.36) [r^2: 0.98; p: 0.27]	0.7

CL, confidence limits.

[a] ED_{50} values were determined from the fraction of rats achieving a biologically significant (>20 ng/ml) prolactin elevation using two to three doses over a 4- to 16-fold range.

[b] ED_{50} values were determined from the sigmoidal log dose-receptor occupancy curve (Fig. 1) of best fit by nonlinear regression analysis with the GraphPad Prism program. Note a p value >0.05 means that the data does not systematically deviate from the sigmoidal curve.

prolactin release with the ED_{50} for apomorphine antagonism for each compound. Amisulpride showed an extreme dissociation between the two effects (factor: 21764), followed, at a distance, by risperidone (14 mg/kg), quetiapine (10 mg/kg), and olanzapine (1.7 mg/kg). When the ED_{50} values for apomorphine antagonism are related to the dose-response relations in Table 1, it is evident that compounds showing a wide dissociation between prolactin release and apomorphine antagonism also show high prolactin levels at the doses required for apomorphine antagonism.

D2 Receptor Occupancy in the Pituitary and the Striatum. Individual values and mean curves illustrating the occupancy of D2 receptors in the pituitary gland and the striatum by the four antipsychotics are shown in Fig. 1.

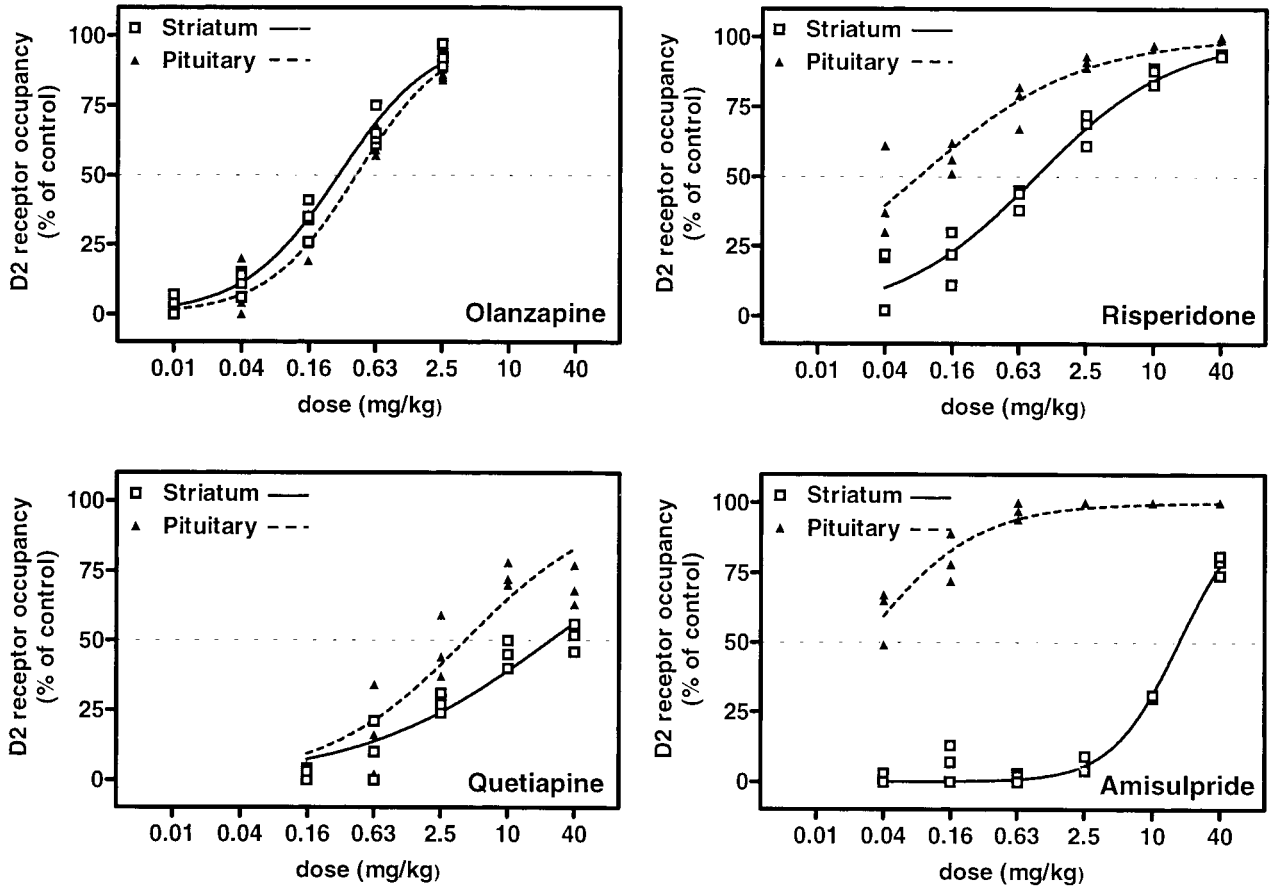

Fig. 1. Individual values and mean curves illustrating the occupancy of D2 receptors in the pituitary gland and the striatum by the four antipsychotics.

Calculated ED_{50} values are listed in Table 2. Among the four tested compounds, the most potent for occupying the central D2 receptors was olanzapine (ED_{50}, 0.30 mg/kg), followed closely by risperidone (0.89 mg/kg) and, at 20 to 80 times higher doses, by amisulpride (17 mg/kg) and quetiapine (24 mg/kg). Regarding the occupancy of D2 receptors in the pituitary gland, the potency order (ED_{50}) was: amisulpride (0.026 mg/kg), risperidone (0.081 mg/kg), olanzapine (0.43 mg/kg), and quetiapine (4.1 mg/kg). For the four compounds, the ratio of the ED_{50} measured in the striatum to that determined in the pituitary corresponded very closely to the dissociation between antagonism of apomorphine-induced stereotypy and induction of prolactin release. A similar rank of order of dissociation between central and peripheral D2 receptor occupancy was obtained (ED_{50} striatum/ED_{50} pituitary): amisulpride (654), risperidone (11), quetiapine (6), and olanzapine (0.7).

Discussion

Our data show that while antipsychotics give rise to a dose-dependent increase in prolactin elevation, a higher peripheral to central dopamine D2 receptor occupancy is the most straightforward explanation as to why some atypical antipsychotics elevate prolactin in the clinical dose range and the others seem not to.

We are not aware of any previous study that has systematically addressed this question; however, several previous preclinical findings are consistent with our observations. Although there are no animal studies regarding the prolactin effects of amisulpride, data on sulpiride, a chemically related substituted benzamide, are informative. When sulpiride was initially used clinically in low doses, it was thought to be devoid of central antipsychotic activity and was observed to give rise mainly to prolactin elevation (O'Connor and Brown, 1982). Once its poor blood-brain penetration was recognized (Rich, 1984), it was used in higher doses clinically and was seen to be effective as an antipsychotic.

Several well-documented clinical findings can now be better understood in light of this study. In human studies, it is not possible to measure pituitary dopamine D2 occupancy due to the limited resolution of the SPECT and PET scanners. Nonetheless, several researchers have used striatal D2 occupancy as a proxy measure of pituitary occupancy and attempted to relate prolactin elevation to striatal D2 occupancy. All these studies have established a relationship between higher D2 occupancy and higher prolactin elevation (Nordstrom et al., 1992; Bench et al., 1996; Kapur et al., 2000). However, the precise level at which striatal occupancy begins has varied considerably from one drug to the other (Nordstrom et al., 1992; Bench et al., 1996; Kapur et al., 2000). Given the severalfold variation across antipsychotics with reference to their central to peripheral ratios shown here, it is not surprising that no absolute relationship between central occupancy and prolactin elevation has been or could logically be shown. This may also explain why a number of previous efforts to use prolactin elevation as a clinical marker of central antipsychotic effects have failed (Smith et al., 1984). Accordingly, the findings of this study also help us to understand why the addition of an antipsychotic with a high peripheral occupancy (sulpride) to an atypical antipsychotic that does not by itself give rise to prolactin elevation (clozapine) would lead to prolactin elevation by the combination (Shiloh et al., 1997; Henderson et al., 2001; Kapur et al., 2001). In addition, our study suggests that the level of prolactin elevation cannot, by itself, be used as a sole criterion for differentiating typical and atypical antipsychotics. The low incidence of EPS, therefore, remains the only criterion that distinguishes all the currently available atypical antipsychotics from their typical counterparts.

Of the four atypical antipsychotics used in this study, amisulpride has the most limited brain penetration and has one of the most intriguing pharmacological profiles. Its proven clinical atypical profile cannot be explained on the basis of a rich receptor pharmacological profile, the main characteristic shared by the other atypical antipsychotics. Consequently, the limited brain penetration of amisulpride may be one of the factors that contributes to its atypical profile. The level of central D2 receptor occupancy (~80%) at which EPS is observed for all major antipsychotics would be more difficult to achieve after administration of amisulpride. The central to peripheral ratio of other antipsychotics should be evaluated in future studies to definitively address the possible relationship between the extent of brain penetration and the atypical profile of antipsychotics with reference to prolactin elevation and EPS.

This finding, then, has important implications for the future design of antipsychotics. As long as antipsychotics work by attenuating dopamine transmission, the potential for prolactin elevation will remain. In keeping with this notion, all antipsychotics in this animal study elevated prolactin—as is indeed the situation in humans (Turrone et al., 2002). The difference between the prolactin-elevating and prolactin-sparing antipsychotics is not qualitative but quantitative (Turrone et al., 2002). The closer the central to peripheral ratio of D2 occupancy is to one (or better still zero) the less likely that the drug will elevate prolactin. Not only is it important that the parent compound shows a favorable central to peripheral ratio, but the active metabolites should also be considered. If the metabolites are active at the D2 receptor, it is important that they have a central to peripheral ratio as good as that of the parent, if not better. It seems that this consideration (i.e., the central to peripheral ratio of D2 occupancy) outweighs the impact of other pharmacodynamic considerations such as the modulation of prolactin levels by the serotonin-dopamine interactions in ensuring prolactin-sparing effects.

Is it possible to change the prolactin-elevating properties of currently available atypical antipsychotics? As expected, the addition of a dopamine agonist to ongoing treatment has been shown to reverse prolactin elevation, and this has been successfully achieved without a loss of clinical benefits (Tollin, 2000). Of course, the selected dopamine agonist should have a degree of "peripheral selectivity" to not neutralize the central antipsychotic effect. Another idea, at the preclinical stage, is to modify the brain penetrability of the active moiety by conjugating it to a fatty acid (Baldessarini et al., 2001). This concept has been used in animals for the atypical antipsychotic clozapine to decrease its peripheral adverse effects, and in principle, such an approach could be used for other drugs (Baldessarini et al., 2001).

When extrapolating to the clinical situation from our findings, it is important to note the ways in which the clinical situation differs from our experiment. First, antipsychotics

are used as a chronic treatment, and there is some evidence that with repeated dosing, tolerance develops to the effects of antipsychotic-induced prolactin elevation (Igarashi et al., 1985). The precise mechanism of this tolerance is not known, but there is no reason to believe that changes in the central-peripheral disposition contribute to it. Furthermore, it is also becoming clear that pharmacokinetic variables such as the rate of the rise of plasma levels and the transience of the high plasma levels are also relevant for prolactin elevation (Movin-Osswald et al., 1995). For example, although atypical antipsychotics such as quetiapine, clozapine, olanzapine, remoxipride, and ziprasidone are not associated with sustained prolactin elevation, each of these "prolactin-sparing" atypical antipsychotics is associated with a short-lasting transient prolactin increase immediately after the dose is administered (Crawford et al., 1997; Turrone et al., 2002). Intriguingly, age may also have an effect on the relative prolactin-sparing effects of different atypicals after sustained use. In a pediatric population, clozapine was found to have prolactin-sparing effects similar to those in the adult population, whereas olanzapine had a significantly greater effect on prolactin release, albeit lower than that of haloperidol (Wudarsky et al., 1999). However, with the prolactin-sparing antipsychotics, this increase does not last until the next dose, and therefore, there is no cumulating prolactin elevation over time (Movin-Osswald et al., 1995; Turrone et al., 2002). Thus, although the central to peripheral ratio is probably one of the most important determinants of the prolactin effects of atypical antipsychotics in the clinical situation, it is not the only relevant factor.

In summary, although atypical antipsychotics all share a lowered propensity for motor side effects, they vary in their propensity for prolactin elevation (Kapur and Remington, 2001). This variation is not accounted for by any of the recent theories of atypicality and is best understood as a manifestation of the differential disposition of the drugs across the blood-brain barrier, resulting in differential pituitary versus striatal D2 occupancy. This differential occupancy may be an important marker in the preclinical development of prolactin-sparing antipsychotics. Alternatively, strategies that enhance central penetration of antipsychotics may also alleviate the effect of differential disposition.

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