P-glycoprotein inhibition potentiates the behavioural and neurochemical actions of risperidone in rats

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Abstract

Antipsychotic drugs are the mainstay pharmacotherapy for schizophrenia and related psychiatric disorders. While the metabolic pathways of antipsychotic drugs have been well defined, the role of drug transporters in the disposition and effects of antipsychotic drugs has not been systematically explored. P-glycoprotein has ubiquitous expression in brain endothelial cells and plays a protective role by effluxing substrates for elimination and by limiting their accumulation in the central nervous system. Risperidone and several other antipsychotic drugs are substrates of P-glycoprotein. Increased antipsychotic drug entry into the brain via blockade of the P-glycoprotein transporter may facilitate the amount of available drug to its targets, particularly dopamine receptors. By increasing available antipsychotic drug concentrations, P-glycoprotein inhibition offers a novel means of enhanced drug delivery. This study evaluated whether selective P-glycoprotein transporter inhibition would increase the effects of risperidone on relevant indices of behaviour (catalepsy and locomotion) and neurochemistry (dopamine release and metabolism as measured by in-vivo microdialysis). We administered the P-glycoprotein inhibitor, PSC 833 (100 mg/kg p.o.), to rats prior to administration of risperidone at varying doses (0.01–4.0 mg/kg s.c.). P-glycoprotein inhibition significantly increased risperidone-induced cataleptic effects, blockade of amphetamine-induced locomotion, and effects on dopamine turnover as seen by increased striatal dopamine metabolite levels. These results provide functional evidence concordant with prior data for increased brain levels of risperidone following PSC 833 treatment.

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Introduction

Drug transporters in the blood–brain barrier can be classified in a number of subfamilies, including the multidrug resistance protein (Bauer et al. 2005). A member of the multidrug resistance protein family, P-glycoprotein (P-gp), was the first drug transporter identified in the blood–brain barrier and acts within brain endothelial capillary cells to limit brain entry of compounds with diverse structures, thereby minimizing or preventing their central nervous system effects (Schinkel et al. 1994; Wang et al. 2004).

Risperidone (Ris) is an atypical antipsychotic drug with preferential affinity for 5-HT₂, D₂, α₁, α₂, and H₁ receptors (Leysen et al. 1992; Schotte et al. 1996). In-vitro binding studies have clearly demonstrated that Ris, as well as several other antipsychotic drugs, are substrates of P-gp (Boulton et al. 2002). Moreover, both brain levels and the brain–plasma ratio of Ris and 9-OH-Ris (the major active Ris metabolite) were significantly increased in mice lacking P-gp in the blood–brain barrier compared to their wild-type controls (12 x for Ris and 29 x for 9-OH-Ris) (Wang et al. 2004). Thus, since P-gp plays an important role in regulating brain antipsychotic drug levels, P-gp inhibition may result in increased antipsychotic drug access to the...
Materials and Methods

Animals

Male Sprague–Dawley rats \( n = 128 \); Charles River Laboratories, USA) weighing 275–300 g were individually housed on a 12-h reverse light cycle (lights off 07:00 hours). Animals were habituated to the vivarium and handled for at least 6 d before surgery. Separate groups of animals were used for the behavioural and microdialysis experiments. All experimental procedures were approved by the Institutional Animal Care and Use Committee of the Medical University of South Carolina and conformed to federal guidelines as described by the Institute of Laboratory Animal Resources on Life Sciences, National Research Council.

Surgery

Animals used for microdialysis were anaesthetized with a mixture of ketamine hydrochloride (66 mg/kg i.m.), xylazine (1.33 mg/kg i.m.), and equithesin (0.5 ml/kg i.p.). Animals were placed in a stereotaxic frame (Stoelting, USA) and implanted with a unilateral stainless-steel guide cannula (20-gauge, 5 mm, Plastics One, USA) in the dorsal striatum using the following coordinates (in mm): AP + 0.8, L ± 3.5, DV −3.4 (Paxinos & Watson, 1997). The cannula was secured to the skull using jeweller’s screws and dental acrylic. After surgery, a stylet was placed into the cannula to prevent blockage and animals were allowed to recover for at least 7 d.

Drugs

PSC 833 (generously provided by Novartis Pharmaceuticals, USA) was dissolved in a mixture of saline, ethanol, and cremophor EL (16:1:1, v/v). Ris (a generous gift from Janssen Pharmaceuticals, USA) was dissolved in 0.5% acetic acid and brought to a final pH of 5.5 with sodium hydroxide. D-amphetamine (Sigma-Aldrich Co., USA) was dissolved in a mixture of saline, ethanol, and cremophor EL (16:1:1, v/v). PSC 833 (generously provided by Novartis Pharmaceuticals, USA) was dissolved in saline, while studies on PSC 833-induced increases in brain Ris levels have used the high end of the dose–response range (Grimm & See, 1998; Ichikawa & Meltzer, 2000), while studies on PSC 833-induced increases in brain Ris levels have used the high end of the dose–response curve, including the dose of 4.0 mg/kg in rats (DeVane et al. unpublished observations).

Behavioural assessments

Locomotion

Locomotor activity was measured in Plexiglas open-field activity boxes (22 × 43 × 33 cm; Columbus, USA). Each chamber was equipped with a monitor (Omnitech Electronics, USA) containing 16 photobeams (eight on each horizontal axis) that tabulated total distance (cm) travelled. Beam breaks were detected by a Digiscan.
analyser and recorded by DigiPro software (version 1.4). The initial measurement of response to the novel test environment involved placing the animals directly into the boxes immediately after injection of Ris or vehicle and recording locomotor activity for 3 h. Animals then received an injection of amphetamine and were returned to the activity boxes for an additional 2 h of recording.

Catalepsy

Two different tests were used to measure catalepsy: a bar catalepsy test and the paw retraction test (Ellenbroek & Cools, 1988; Kruzich & See, 2000). For bar catalepsy, the animal was placed with the front paws onto a steel bar (1 cm diameter) set at a height of 8 cm. The latency to remove at least one paw from the bar served as the dependent measure. The minimum and maximum scores for this test were designated at 1 s and 120 s, respectively. For the paw retraction test, we utilized an elevated Plexiglas box with 4-cm diameter holes for the forelimbs and 5-cm diameter holes for the hindlimbs. During a test, the hindlimbs were gently placed into the 5-cm holes, followed by placing the forelimbs into the 4-cm holes. The latencies to remove one forelimb and one hindlimb were recorded separately and served as dependent measures for this test. The minimum score for the paw test was 1 s and the maximum possible score was 60 s.

Microdialysis probes were constructed with dialysis membrane (250 µm outer diameter; 3 mm length), based on previously described methods (Robinson & Whishaw, 1988). The probe was inserted 16–18 h prior to beginning sample collection. Dialysis probes were perfused with modified Ringer’s solution (NaCl, 147 mM; CaCl₂, 1.8 mM; KCl, 2.7 mM; MgCl₂, 1.2 mM; Na₂HPO₄, 0.5 mM; adjusted to pH 7.4) at a rate of 2 µl/min. Perfusate samples were collected in 10 µl of mobile phase. Three consecutive samples were collected at 20-min intervals and served as the baseline, with additional samples collected every 20 min for 4 h.

HPLC

Microdialysis samples were stored at −80 °C before being analysed by HPLC with coulometric detection. Samples were injected by an autosampler (ESA model 542, Chelmsford, USA) onto a reverse-phase column (MD150, ESA) maintained at 30 °C. Mobile phase consisted of 90 mM sodium dihydrogen phosphate, 50 mM citric acid, 1.7 mM 1-octanesulfonic acid, 50 µM EDTA, and 10% acetonitrile (final pH 3). Coulometric detection (Coulochem Detector III, Microdialysis cell 5014B, ESA) was used to identify DA, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA). Three electrodes were used: a guard cell (350 mV), a reduction analytical electrode (−150 mV), and an oxidation analytical electrode (200 mV). Peaks were recorded and peak heights were measured by a computer using ESA chromatography data system. Analyte concentrations were determined by comparing peak heights with a standard curve.

Experimental design

Behaviour

One hour after receiving PSC 833 (100 mg/kg p.o.), animals received Ris (0, 0.4 or 4 mg/kg s.c.) and were then placed into the activity boxes to measure the effect of Ris on locomotor response to the novel environment. Bar catalepsy and paw retraction were consecutively measured at 60, 180, and 300 min after Ris injection. For these tests, animals were removed for not more than 5 min and then immediately returned to the activity boxes. After the initial 3 h of locomotor measurement, all animals received an injection of d-amphetamine (1 mg/kg i.p.) and were then returned to the activity boxes for an additional 2 h of recording.

Microdialysis

A microdialysis probe was lowered into the guide cannula the day before the microdialysis experiment, and probes were perfused overnight at a flow rate of 0.2 µl/min. The next morning, the flow rate was increased to 2.0 µl/min and collection started 90 min later in order to allow establishment of stable baseline levels. After collecting three baseline samples, animals received PSC 833 (100 mg/kg) or vehicle via oral gavage. One hour later, animals received Ris (0, 0.01, 0.4, or 4 mg/kg s.c.). Microdialysis samples were collected every 20 min for an additional 3 h.

Histology

Immediately following microdialysis collection, animals were euthanized by rapid decapitation. The brains were then extracted and stored in a 10% formaldehyde solution. Brains were coronally sectioned (75 µm), mounted onto slides, and sections then stained with Cresyl Violet in order to verify probe placement. As shown in Fig. 1, assessment of dialysis probe placement showed that probes were localized in the dorsal striatum (caudate putamen). Animals that
did not have proper probe placement were not utilized in the data analysis.

**Data analysis**

Behavioural data were analysed using two-way analysis of variance (ANOVA), followed by *post-hoc* comparisons using the Student–Newman–Keuls test. For microdialysis, basal extracellular concentrations were determined and post-injection values were then converted to percentage of the baseline. Data were then analysed with two-way repeated-measures ANOVA (rm-ANOVA) to assess the percent change from baseline for DA, DOPAC, HVA, and 5-HIAA following Ris injection at each of the different doses, followed by *post-hoc* comparisons with the Student–Newman–Keuls test. All analyses were considered statistically significant at $p < 0.05$. Only statistically significant effects are described in the Results section. All data are presented as mean $\pm$ S.E.M.

**Results**

**Locomotor activity**

Figure 2 shows Ris inhibition of locomotor activity during the response to the novel environment, as well as inhibition of amphetamine-induced locomotion. The top panels represent the total distance travelled for 3 h after Ris injection (Fig. 2a) and for the 2 h after amphetamine injection (Fig. 2b). The temporal course of locomotor activity over the entire 5 h test period is shown in Fig. 2c. Due to the profound inhibition produced by both doses of Ris over the first 3 h [significant for dose: $F(2, 46) = 31.66$, $p < 0.001$], PSC 833 pretreatment (100 mg/kg p.o.) did not significantly affect Ris-induced inhibition of the response to the novel environment. However, PSC 833 significantly potentiated Ris inhibition of amphetamine-induced locomotion. Significant effects were seen for PSC 833 pretreatment [$F(1, 46) = 5.14$, $p < 0.05$] and Ris dose [$F(2, 46) = 8.69$, $p < 0.001$]. Separate analyses for each dose of Ris revealed that PSC 833 enhanced Ris inhibition of amphetamine-induced locomotion (Fig. 2b).

**Catalepsy measurement**

Figure 3(a–c) shows data for bar catalepsy, forelimb retraction, and hindlimb retraction, respectively. PSC 833 potentiated and prolonged the duration of Ris-induced catalepsy, with significant main effects found for PSC 833 pretreatment [$F(1, 38) = 18.72$, $p < 0.0001$], Ris dose [$F(2, 38) = 54.19$, $p < 0.0001$], pretreatment x Ris dose [$F(2, 38) = 6.86$, $p < 0.005$], and pretreatment x Ris dose x time [$F(4, 76) = 2.63$, $p < 0.05$]. *Post-hoc* analyses revealed that catalepsy induced by 4.0 mg/kg Ris was significantly elevated by PSC 833 at 180 and 300 min after treatment. In fact, catalepsy decreased over time in the absence of PSC 833 pretreatment, but increased over time in animals given PSC 833.

In the paw retraction test, PSC 833 not only potentiated and prolonged the latency to remove a paw, but also altered Ris-induced response patterns. Previous studies have shown that Ris produces a preferential dose-dependent effect on increasing hindlimb retraction latencies (Grimm & See, 1998), which is believed to reflect an atypical antipsychotic.
drug profile (Ellenbroek & Cools, 1988). However, PSC 833 pretreatment prior to Ris produced an increase in both forelimb and hindlimb latencies. For forelimb retraction, significant main effects of pretreatment \[ F(1, 39) = 14.57, p < 0.0001 \] and Ris dose were seen \[ F(2, 39) = 32.68, p < 0.0001 \], as well as significant interactions for pretreatment × Ris dose \[ F(2, 39) = 9.83, p < 0.0001 \] and pretreatment × Ris dose × time \[ F(4, 78) = 5.21, p < 0.005 \]. Post-hoc analyses for forelimb retraction showed increased retraction times after PSC 833 + Ris 4.0 at all three time-points. In addition, at 180 min, PSC 833 + Ris 0.4 produced significantly greater retraction times than vehicle + Ris 0.4, while at 300 min, PSC 833 + Ris 4.0 was significantly higher than Ris 4.0 alone.

**Microdialysis**

Basal concentrations of analytes did not differ between groups. Basal values in nM (means ± S.E.M.) were DA = 1.46 ± 0.09; DOPAC = 512.44 ± 37.03; HVA = 450.72 ± 30.32, and 5-HIAA = 63.62 ± 3.93. Figures 4–6

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**Fig. 2.** PSC 833 pretreatment potentiates risperidone (Ris) inhibition of amphetamine (Amph)-induced locomotion. Animals \( (n = 6–9 \text{ per group}) \) received PSC 833 (100 mg/kg p.o.), followed 1 h later by Ris (0, 0.4, or 4 mg/kg s.c.). Locomotor activity (recorded in 10-min intervals) in response to the novel test environment was measured for 3 h, at which time animals received an Amph challenge (1 mg/kg i.p.). Total distance travelled is shown for (a) the response to novelty phase and (b) after the Amph challenge. Significant differences from vehicle (Veh) pretreatment are indicated (* \( p < 0.01 \)). (c) Illustrates the entire time-course for each group over the 5-h testing period.
As seen in Fig. 4a, PSC 833 alone had no effect on DA efflux. Ris at the 0.01 dose had no significant effect (Fig. 4b), but a significant effect over time was seen for the 0.4 [F(13,279)=2.33, p<0.01] and the 4.0 [F(13,265)=7.54, p<0.001] doses of Ris (Fig. 4c, d) in the presence of PSC 833 pretreatment. Post-hoc analyses showed significant increases over baseline for Ris 4.0 (Fig. 4d). Measurement of DOPAC indicated robust increases over time at all three doses of Ris (Fig. 5). For Ris 0.01 (Fig. 5b), a significant effect of time [F(13,335)=6.12, p<0.001] and pretreatment \times time interaction [F(13,335)=2.96, p<0.001] were found, with significant increases over baseline only in the PSC 833 pretreated group, as well as when compared to the vehicle pretreated group at several time-points. For Ris 0.4 (Fig. 5c), we found a significant effect of time [F(13,307)=44.15, p<0.001] and a pretreatment \times time interaction [F(13,307)=5.59, p<0.001]. For multiple time-points, analyses revealed significant increases over baseline in both groups, and in the PSC 833+Ris 0.4 group over Ris 0.4 alone. For Ris 4.0 (Fig. 5d), ANOVA showed only a significant effect of time [F(13,307)=16.17, p<0.001], and a lack of differences between groups. Changes in HVA levels mirrored those seen in DOPAC, but to a lesser extent (Fig. 6). Interestingly, a slight, but significant effect of time [F(13,279)=3.66, p<0.001] was seen for the no Ris condition (Fig. 6d). For Ris 0.01 (Fig. 6b), a significant effect of time [F(13,321)=12.28, p<0.001] and a pretreatment \times time interaction [F(13,321)=2.03, p<0.05] were found, with significant changes over baseline only seen in the PSC 833 pretreated group, and a significant increase in the PSC 833 pretreated group over vehicle at 240 min. For Ris 0.4 (Fig. 6c), we found a significant effect of time [F(13,307)=13.38, p<0.001], with multiple time-points elevated over baseline in both groups. A similar pattern was seen after Ris 4.0 (Fig. 6d), with a significant effect of time [F(13,307)=33.52, p<0.001] and several points showing elevations over baseline.

**Discussion**

The present study for the first time characterized both behavioural and neurochemical effects of P-gp inhibition on *in-vivo* antipsychotic drug actions in the brain. Specifically, we found that inhibition of P-gp with PSC 833 potentiated Ris blockade of amphetamine-induced locomotion and increased both the magnitude and duration of Ris-induced catalepsy. At a neurochemical level, we showed that P-gp inhibition modestly facilitated Ris-induced DA turnover, as seen by increased levels of DA metabolites after PSC 833.
pretreatment compared to vehicle pretreatment. Prior evidence has shown that lowering P-gp activity, either by using P-gp knockout mice (Kirschbaum et al. 2008; Wang et al. 2004) or by P-gp inhibitors (Wang et al. 2006), increased tissue levels of Ris. Thus, although not directly measured in vivo in the present study, we can infer that the effects noted in the present study are due to elevated Ris and 9-OH Ris levels in the brain.

The inhibition of amphetamine-induced hyperlocomotion is a widely accepted behavioural model of limbic hyperdopaminergic activity (Ogren, 1996), and serves as a predictive assay to screen potential compounds for antipsychotic drug activity. Catalepsy, on the other hand, is a measure of motor inhibition induced by antipsychotic drugs, and has long been viewed as an indicator for neuroleptic-induced extrapyramidal motor side-effect liability (Janssen et al. 1965). P-gp inhibition by PSC 833 potentiated the effects of Ris on both measures, indicating the functional effects of PSC 833 on different neural substrates. Of particular note was the prolongation of Ris effects by PSC 833, whereby the effects of high dose Ris had generally dissipated after 5 h in the absence of PSC 833 pretreatment, but remained essentially unchanged in the presence of PSC 833. While these behavioural measures in rats constitute an important first step in examining P-gp inhibitors for their enhancement of antipsychotic drug effects, there are limitations in extrapolating this data to antipsychotic drug effects in humans. However, our results provide functional evidence that the co-administration of PSC 833 with Ris may increase the efficacy of Ris treatment and allow lower systemic doses to obtain desired effects. It will be important to closely study the dose range for combined P-gp inhibitors and antipsychotic drugs in order to maximize the antipsychotic effects, while avoiding the increased motor side-effects seen at high doses. In humans, clinically established lower doses of Ris can be used compared to those used in animal models (Davis & Chen, 2004), thus minimizing possible motor side-effects produced by increased Ris brain levels in the presence of P-gp inhibitors. Future examination of other atypical antipsychotic drugs with low motor side-effects that serve as substrates for P-gp transport (e.g. aripiprazole) will be important for assessment during P-gp inhibition. Additional
Preclinical assessments of efficacy used in animal models, such as prepulse inhibition of the startle response (Swerdlow et al. 2001), will also be important measures for future examination of potentiated antipsychotic drug effects via P-gp inhibition. Finally, it is important to note that P-gp inhibition can increase the brain penetrance of multiple agents, not just the targeted drug (e.g. Ris). Any eventual clinical application of P-gp inhibitors will need to fully consider non-selective drug actions.

Surprisingly, P-gp inhibition in the present study did not enhance striatal DA release, even at doses of PSC 833 known to increase brain Ris levels (DeVane et al. unpublished observations). DA levels increased in the presence or absence of PSC 833 pretreatment and returned to baseline fairly soon after Ris injection. Previous reports have noted somewhat limited effects of Ris on DA release, even at high doses of the drug (Grimm & See, 1998; Volonte et al. 1997). Such patterns may relate to non-dopaminergic effects of the drug that can alter DA signalling, especially as Ris has high affinity for serotonin and noradrenergic receptors (Leysen et al. 1992). In contrast to DA efflux, PSC 833 pretreatment significantly increased DA metabolism produced by Ris administration. It has been shown that the mechanisms regulating extracellular levels of DA and DA metabolites lack a direct relationship (See et al. 1995; Zetterstrom et al. 1986). As DOPAC levels largely reflect intraneuronal DA metabolism (Zetterstrom et al. 1988) of newly synthesized DA (Soares-da-Silva & Garrett, 1990), the increase in Ris levels via PSC 833 appears to enhance DA turnover in striatal terminals, probably through enhanced blockade of presynaptic DA receptors (Zetterstrom et al. 1986, 1988). Alternatively, other antipsychotic drugs (e.g. haloperidol) have been found to alter DOPAC transport (Commissiong, 1985). While not yet known, such a mechanism may also occur with Ris. The lack of differences at the high Ris dose (4 mg/kg) may be due to ceiling effects of elevated DOPAC and HVA levels. In addition, compensatory changes at very high levels of Ris may have obscured PSC 833 effects.

Fig. 5. PSC 833 pretreatment potentiates risperidone (Ris)-induced striatal 3,4-dihydroxyphenylacetic acid (DOPAC) increases. Extracellular DOPAC levels (n=8–12 per group) expressed as percent of the baseline following either vehicle (Veh) or PSC 833 pretreatment (100 mg/kg) for Ris (0–4 mg/kg): (a) 0, (b) 0.01, (c) 0.4 and (d) 4.0. Significant differences from baseline (* p<0.05) or between Veh and PSC 833 pretreatment (’ p<0.05) are indicated.
Given the notable long-lasting behavioural effects of PSC 833 pretreatment, microdialysis sampling for longer time periods may reveal persisting actions of Ris on elevated DA turnover after PSC 833 pretreatment.

While the present results clearly indicate behavioural and neurochemical effects of P-gp inhibition on Ris effects in vivo, they do not offer conclusive information on the relationship between measures of locomotion/catalepsy and DA release and turnover. Indeed, these measures have generally not been well correlated in the past (See & Chapman, 1994), probably due to the fact that DA receptor antagonist action on post-synaptic receptor-mediated signalling plays a more critical role in the direct effects of antipsychotic drugs (Farde et al. 1992). Thus, the current measures should be viewed as parallel lines of information on the impact of P-gp inhibition on Ris-mediated effects. Future studies may examine a number of antipsychotic drug-sensitive measures that could be affected by P-gp inhibition. In addition to the use of additional behavioural tasks, it would be highly informative to examine whether PSC 833 modifies Ris occupancy of DA and serotonin receptors, affects other neurotransmitter systems, and leads to changes in the neuronal firing properties of DA and other neurons.

In summary, the present results provide new evidence for the enhancement of antipsychotic drug actions in the brain via P-gp inhibition. Along with previous pharmacokinetic evidence (Wang et al. 2004; Zhu et al. 2007), these results suggest that selectively inhibiting P-gp activity in the central nervous system may alter treatment outcomes by increasing available antipsychotic drug levels at target receptors. Of considerable advantage would be the concomitant reduction in systemic drug levels through the use of reduced overall doses. Since antipsychotic drugs often precipitate various side-effects (e.g. diabetes, hyperglycaemia, and lipid dysregulation) that impact other organ systems (Newcomer, 2005), continued development and application of P-gp inhibitors offers potential clinical advantages for chronic pharmacological treatment of schizophrenia and related disorders.

Fig. 6. PSC 833 pretreatment potentiates risperidone (Ris)-induced striatal homovanillic acid (HVA) increases. Extracellular HVA levels (n = 8–12 per group) expressed as percent of the baseline following either vehicle (Veh) or PSC 833 pretreatment (100 mg/kg) for Ris (0–4 mg/kg): (a) 0, (b) 0.01, (c) 0.4 and (d) 4.0. Significant differences from baseline (\( ^\ast p < 0.05 \)) or between Veh and PSC 833 pretreatment (\( ^\dagger p < 0.05 \)) are indicated.
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Statement of Interest

None.

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