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ORIGINAL INVESTIGATION

Orthostatic hypotensive effect of antipsychotic drugs in Wistar rats by in vivo and in vitro studies of α_1-adrenoceptor function

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Abstract
Rationale Many antipsychotics cause orthostatic hypotension possibly due to antagonist action on resistance vessel α_{1A}-adrenoceptors (α_{1A}-AR).
Objective We have tested this possibility by determining in Wistar rats how the orthostatic hypotensive effect of several antipsychotic drugs compares with their affinity for adrenoceptors in mesenteric small arteries (MSA with mainly α_{1A}-AR) and aorta (mainly α_{1D}-AR).
Materials and methods Using a tilt setup, orthostatic hypotension was measured in anaesthetized rats for prazosin and the antipsychotics haloperidol, sertindole, risperidone, clozapine, ziprasidone, domperidone, olanzapine, and aripiprazole. For in vitro studies, segments of MSA and aorta were mounted on a wire myograph for isometric tension recording. Cumulative concentration-response curves were constructed to phenylephrine (PE) in the absence and presence of the drugs. Apparent affinity (pA_2) was calculated by Schild analysis.
Results Prazosin antagonized tilt-induced and PE responses in both studies (threshold 4 ng/ml, pA_2 9.52 MSA, 10.1 aorta). The rank order of the potency of the antipsychotics in the tilt experiments correlated (r^2=0.69, P=0.01) with the pA_2-values in MSA: Risperidone and sertindole had the highest potency in the tilt test (threshold 159 and 97 ng/ml) and the highest apparent affinity in MSA (pA_2 8.92 and 8.78), in contrast with aripiprazole and domperidone, which had the lowest in each case (threshold 4.1 and 3.0 μg/ml, pA_2 7.17 and 6.99). In aorta, the pA_2 values did not correlate with the in vivo potencies; in particular, sertindole had no functional affinity in aorta.
Conclusion We conclude that the orthostatic hypotensive effect in rats of the antipsychotic drugs investigated is mediated through α_{1A}-ARs.

Keywords Antipsychotic drugs · α_1-Adrenoceptors · Small mesenteric artery · Aorta · Tilt model · Rat

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Introduction

Antipsychotic drugs are used in the treatment of schizophrenia, a common psychotic disease that affects around 0.7–1% of the world population (Williams et al. 2004). Almost all available antipsychotic drugs are dopamine D_2-receptor antagonists, and it is generally accepted that antipsychotic effects are mediated through blockade of mesolimbic D_2 dopaminergic receptors (Lewis and Lieberman 2000). Nevertheless, most antipsychotic drugs have effects on other receptors such as serotonin 5-HT_2 receptors, muscarinic (M_2) receptors, and α-adrenoceptors, particularly α_1-adrenoceptors (Buckley and Sanders 2000; Svensson 2003). Extrapyramidal side effects (EPS) in patients under treatment with typical antipsychotic drugs such as haloper-

idol are mediated via striatal dopamine D_2 receptor blockade (Lidow et al. 1998). These side effects are reduced for the atypical drugs such as clozapine, possibly because of lower affinity of atypical antipsychotics for D_2-receptors and greater affinity for $5HT_2$-receptors (Strange 2001).

In addition to EPS, the atypical antipsychotics like the typical ones frequently have cardiovascular side effects such as increase in the QT interval of the electrocardiogram and orthostatic hypotension (Buckley and Sanders 2000). The latter may be caused by their antagonist action against α_1-adrenoceptors (α_1-AR). The importance of the α_1 component of these drugs as regards their antipsychotic effects has been studied intensively (Lane et al. 1988; Prinssen et al. 1994; Wadenberg et al. 2000). However, the role of α_1-AR subtype with respect to their cardiovascular side effects, especially orthostatic hypotension, has received little attention, and to our knowledge, there are no data to show a direct comparison between in vivo and in vitro effects of antipsychotics. We have therefore investigated the hypothesis that the ability of antipsychotic drugs to cause orthostatic hypotension is correlated to their α_1-AR antagonist affinity (especially α_{1A}-AR) on resistance vessels.

The hypothesis has been tested by comparing the rank order of a range of antipsychotic drugs both in vivo in an animal tilt model of orthostatic hypotension (Take et al. 1998; Hashimoto et al. 1999; Hieble et al. 1999; Akiyama et al. 2002; de Moura et al. 2005), and in vitro using isolated rat mesenteric small arteries (MSA) studied in a myograph (Mulvany and Halpern 1977). These latter vessels are important in the control of blood pressure (Fenger-Gron et al. 1995) and contain mainly α_{1A}-AR (Ipsen et al. 1997). In the in vivo experiments, the rank order of the drugs was based on the lowest concentration to give a detectable orthostatic hypotension response. In the in vitro experiments, rank order was based on the apparent affinity (pA_2) of the drugs for α-AR, determined using Schild analysis of the contractile responses to PE. For comparison, we also studied the α-AR affinities in rat thoracic aorta, a vessel containing predominantly α_{1D}-AR (Hussain and Marshall 1997; Marti et al. 2005).

Materials and methods

This study was conducted in accordance with the current Danish Animal Testing Act.

In vivo experiments

Tilt setup

Male normotensive Wistar rats (220–250 g) were anesthetized with administration of pentobarbital (1%, 50 mg/kg) intraperitoneally, in a volume of 5 ml/kg. During the surgical implantation of the catheters, the anesthesia was supplemented with isoflurane. The left common carotid artery was cannulated with a polyethylene tube to monitor the systemic arterial pressure and for final blood sampling. Systemic arterial pressure was monitored by a pressure transducer (SensoNor 844, SensoNor, Norway) placed at the heart level so that the tilting itself did not influence blood pressure measurement. The left jugular vein was cannulated for administration of test drugs or vehicle. Then, the rats were fixed in the supine position with the fulcrum of the customized tilt table at the level of the heart.

In vivo experimental procedure

Observation of the tilt-induced blood pressure response in rats has previously been described (Take et al. 1998; Hashimoto et al. 1999; Hieble et al. 1999; Akiyama et al. 2002; de Moura et al. 2005). In this study, the method has been customized as follows. Rats were rapidly (within 1–2 s) subjected to a consistent 60° head-up tilt from the horizontal position. This was considered as the pre-dose tilt. If a normal blood pressure response was not observed (immediate tilt-induced blood pressure <85% of pre-tilt blood pressure and compensatory blood pressure response >90% of pre-tilt blood pressure) within three pre-dose tilts (10 min apart), the rat was omitted from the study. If more than one pre-dose tilt was performed, the final tilt was used in the analysis. Vehicle or test drugs were administered 5 min after the pre-dose tilt. A similar post-dose tilt was initiated 10 min after the test drug had been administered. Each tilt was timed to last 60 s.

Each rat was injected once intravenously (i.v.) with one of ten different compounds: vehicle (10% hydroxypropyl-β-cyclodextrin, HPβC), prazosin (0.0011 to 0.044 mg/kg), clozapine (0.1 to 3 mg/kg), ziprasidone (0.01 to 1 mg/kg), sertindole (0.1 to 5 mg/kg), aripirazol (1 to 30 mg/kg), haloperidol (0.3 to 10 mg/kg), risperidone (0.01 to 1 mg/kg), olanzapine (0.01 to 3 mg/kg), and domperidone (0.3 to 10 mg/kg). Each drug was tested at three to six dose levels (two to five animals per dose level). Blood samples were collected immediately after the end of the post-dose tilt for measurement of drug plasma concentrations.

Analysis of drug plasma concentration

Analysis of plasma concentration for all tested drugs was performed using turbulent flow chromatography followed by detection using mass spectrometry (API 3000, MDS Sciex, Canada) according to a method described early (Sanchez and Kreilgaard 2004). The concentration of compounds in plasma was determined by standard calibration curves (1–1,000 ng/ml) for each analysis prepared

using ethylene diamine tetra-acetic acid (EDTA)-treated plasma from untreated animals.

In vivo data analysis

Continuous recording of blood pressure and mean arterial blood pressure (MAP) was performed. Exact values were measured immediately before tilt (baseline at 0 s) and at 2, 5, 10, 20, 30, 40, 50 and 60 s after the start of tilt. Due to marked fall in MAP caused by i.v. injections of the test drugs, the tilt response was expressed with reference to the baseline value before the tilt (100%) plotted against time after the start of tilt, from which the area under the curve from 0 to 60 s ($AUC_{0–60}$) was calculated. The effect of the dose of test drug on the tilt response was taken as $\Delta AUC_{0–60}$=$AUC_{0–60}$ (pre-dose tilt)-$AUC_{0–60}$ (post-dose tilt). All values are presented as mean ± SEM.

Statistical analyses of data were performed using a computer program (GraphPad Prism, San Diego, CA, USA). A nonparametric test (Kruskal-Wallis) was used for each drug to simultaneously determine significance over all dosing levels. If there was overall significance, individual comparisons were made to determine the possible significance of differences at each dosing level, compared to vehicle (Dunn's test). Statistical significance was set at $p<0.05$. In the vehicle-administered animals, the pre-dose tilt was compared to the post-dose tilt by a Student's *t* test. For each drug, the plasma concentration of the lowest dose that was found to be significantly different from vehicle has been selected as an estimate of the potency of each drug and, thereby, to generate the rank order between the drugs.

In vitro experiments

Rat isolated small mesenteric artery and aorta preparation

Male Wistar rats (300–350 g) were killed by cervical dislocation, after which the mesentery or the aorta was removed immediately and placed in cold physiological salt solution (PSS 4°C) of the following composition (mM): NaCl 119, KCl 4.7, $CaCl_2$ 1.6, $MgSO_4.7H_2O$ 1.17, $NaHCO_3$ 25, glucose 5.5, KH_2PO_4 1.18, and EDTA 0.026. The solution was gassed with 5% CO_2 in air. Segments of thoracic aorta and mesenteric small arteries (approximately 2 mm) cleaned of surrounding adipose tissue were mounted as ring preparations on two 100- or 40-μm wires, respectively, in a wire myograph (J.P. Trading, Aarhus, Denmark). The vessels were allowed to equilibrate in PSS (thermostatically controlled at 37±0.5°C for at least 30 min).

After the stabilization period, the internal diameter of each vessel was set to an extension equivalent to 0.9 times the estimated diameter at 100 mmHg effective transmural pressure (l_{100}=200–250 μm) according to the standard procedure of Mulvany and Halpern (1977). After examination of viability of vessels, as described below, the endothelium was removed by gently rubbing the lumen with a hair to confirm that the main function of the antipsychotic drugs was the result of their action on smooth muscle cells not on the endothelium. Removal of the endothelium was confirmed by the presence and absence of relaxation to acetylcholine (ACh, 10^{-5} M), before and after removal, in mesenteric arteries precontracted with noradrenaline (NA, 10^{-5} M). The presence of endothelium in rat thoracic aorta, before and after removal, was tested using phenylephrine (PE) 10^{-6} M as preconstrictor then ACh (3×10^{-6} M). Experiments were only performed on vessels that showed less than 10% relaxation after endothelial removal. In some experiments, where indicated, the endothelium was not removed.

Experimental procedure

Mesenteric small arteries

After standardization of the internal diameter, the viability of vessels was examined by exposing them to NA 10^{-5} M three times, 2 min per activation, with washouts after each exposure. As described above, the function of the endothelium was assessed after the third exposure to NA. After removal of endothelium, the vessels were incubated with propranolol (10^{-6} M) and cocaine (3×10^{-6} M) for at least 10 min to block β-AR and neuronal uptake of NA, respectively.

Initially, a PE concentration-response curve was obtained by adding PE from 0.02 to 640 μM in twofold increments to the bath every 2 min. The vessels were then washed to baseline and incubated with test drug for 30 min. A new concentration–response curve for PE was constructed in the presence of the drug. Only one concentration of the drug was used for each vessel.

Aorta

The standard start for testing the viability of aorta preparations was made by exposing them to NA (10^{-6} M) three times for 3 min per activation. After testing the function of endothelium and its removal, as described above, a curve for PE (3×10^{-9} M to 3×10^{-5} M) was constructed in control condition (with vehicle) and in the presence of propranolol (10^{-6} M), and yohimbine (10^{-7} M), cocaine (6×10^{-6} M), and corticosterone 21-acetate (CCA, 10^{-6} M) to block β-AR, α_2-AR, neuronal, and extra neuronal uptake of NA, respectively. After the washing and incubation of the vessels with antagonist for 30 min,

the second concentration–response curve for PE was constructed as described above.

In vitro data analysis

The mechanical responses of the vessels were measured as force and expressed as active wall tension, which is the increase in measured force divided by twice the segment length (Mulvany and Halpern 1977). Responses are plotted graphically as means from at least four separate experiments (one vessel per animal in each experiment), with vertical lines representing SEM. When error bars do not appear on the figures, this is because they are small and fall within the dimension of the symbols. Curves were fitted (GraphPad Prism, San Diego, CA, USA) to all the data by nonlinear regression to determine Hill slopes for the agonist concentration–response curves and to calculate pD_2 values (−log of the EC_{50} values). The EC_{50} value in the presence and absence of test drug (antagonist) was used to determine the concentration-ratio (CR). pA_2 values were calculated by linear regression by use of the same computer program and were obtained from the *x*-intercept of the plot of log (CR-1) against log molar antagonist concentration (Arunlakshano and Schild 1959). Slope values were evaluated for statistical difference from unity by *t* test. Statistical analysis of concentration-response curves was performed using two-way analysis of variance followed by Bonferroni post-test.

Drugs and solutions

The following drugs were used. Noradrenalinehydrochloride (HCl), L-phenylephrine (HCl) acetylcholine chloride, cocaine (HCl), DL-propranolol (HCl), yohimbine (HCl), corticosterone 21-acetate (CCA), and prazosin (HCl) were all obtained from Sigma (St. Louis, USA). Sertindole, risperidone, clozapine, ziprasidone, aripiprazole, and olanzapine were all synthesized and provided by H. Lundbeck A/S, Denmark. Haloperidol was purchased from Sigma, and domperidone was purchased from Research Biochemical International (RBI, Natick, MA, USA). All drugs for in vitro experiments, unless otherwise stated, were dissolved in double-distilled, deionized water. CCA was dissolved in absolute ethanol and diluted further with 50% ethanol. Prazosin HCl was dissolved initially in 50% ethanol to give a 1 mM stock solution and subsequently diluted in distilled water. Sertindole was dissolved in water including a few drops of 0.1 M HCl, heated to 40°C, then diluted in distilled water. Clozapine, ziprasidone, aripiprazole, and domperidone were dissolved initially in dimethylsulfoxide to a stock of 10 mM, and then diluted in distilled water. Ziprasidone, aripiprazole, and domperidone were diluted in 50% ethanol to a concentration of 1 mM and then diluted with distilled water. Risperidone, haloperidol, and olanzapine were dissolved in absolute ethanol to make a stock solution of 10 mM. Further dilution for risperidone and olanzapine was in distilled water and for haloperidol in 50% ethanol to a concentration of 1 mM, and then further diluted in distilled water. All stock solutions for in vitro experiments were stored frozen in aliquots and thawed and diluted fresh daily. All test drugs for in vivo experiments were dissolved in 10% hydroxypropyl-*β*-cyclodextrin (HPβC) on the day of use and administered in a volume of 1 ml/kg.

Results

In vivo study

The combined use of pentobarbital and isoflurane gave a satisfactory anesthesia that did not suppress the tilt responses. Thus, an almost complete compensation of reflex responses was found to the initial tilt-induced drop in blood pressure during the pre-dose tilt periods in anesthetized rats (pre-dose tilt responses in Fig. 1a). There were no significant differences in the pressure responses between pre-dose and post-dose tilt in the control (vehicle

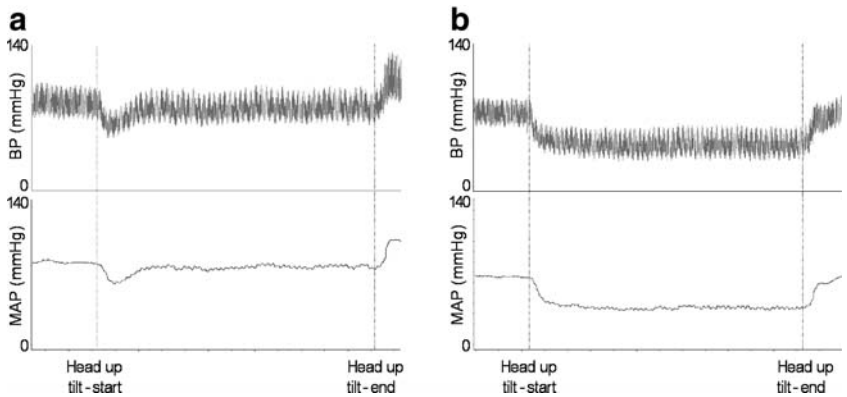

Fig. 1 Effect of risperidone on head-up tilt-induced orthostatic hypotension. Representative tracing of tilt-induced change on blood pressure (*BP*, *upper traces*) and mean arterial blood pressure (*MAP*, *lower traces*) in **a** pre-dose tilt and **b** post-dose tilt after administration of risperidone at 1 mg/kg, i.v. Time from start to end of each tilt was 60 s

administered) animals (Table 1). As seen in Fig. 1b, administration of risperidone (1 mg/kg, i.v.) inhibited the reflex response, which did not reestablish during the 60-s post-dose tilt. ΔAUC_{0-60} values and the mean of plasma concentrations of drugs at the end of tilt procedure are indicated in Table 1. Dose-dependent increases in the ΔAUC_{0-60} values were observed for all drugs except aripiprazole and domperidone. Haloperidol showed a dose-dependent increase in ΔAUC_{0-60}, but the effect was just not statistically significant ($p=0.07$; Tables 1 and 2).

To estimate the drugs' potencies to cause orthostatic hypotension on the tilt setup, we have measured for each drug investigated the plasma concentrations for each dose (Table 1). These measurements were then used to rank the tested drugs based on the plasma concentration of the first dose of drugs having a significant increase in ΔAUC_{0-60} compared with vehicle (see Table 1). As shown in Table 2, prazosin (used as a positive control) has the highest rank followed by sertindole, and thereafter in order risperidone, ziprasidone, olazapine, clozapine, haloperidol, domperidone, and aripiprazole. Figure 2 shows the changes in blood pressure during the 60° head-up tilt for 60 s after administration of various doses of prazosin and risperidone. Prazosin at more than 0.022 mg/kg, i.v., completely depressed the tilt induced blood pressure responses (Fig. 2a, Table 1). Although 0.3 and 1 mg/kg, i.v. administration of risperidone completely depressed the responses, partial compensation was observed at 0.03 and 0.1 mg/kg (Fig. 2b).

In vitro study

Antagonism of PE responses in rat small mesenteric arteries in vitro

In the rat mesenteric small artery, PE produced isometric contraction in a concentration-dependent manner ($pD_2=6.24\pm0.02$, $n=11$). Prazosin shifted the concentration–response curve to PE markedly to the right (Fig. 3a, Table 3). The responses to PE were antagonized by domperidone, risperidone, and sertindole in a concentration-dependent manner with no depression in maximum responses (Figs. 3 and 4, Table 3) and pA_2 values 6.99, 8.92, and 8.78, respectively. None of the Schild slopes differed significantly from unity (Table 3). For sertindole and risperidone, exactly the same results were obtained in vessels where the endothelium had not been removed ($n=12$, data not shown).

The responses to PE were also antagonized by the presence of ziprasidone and aripiprazole (Fig. 5), and clozapine, haloperidol, and olanzapine (data not shown). Schild regression analysis carried out for these drugs against PE gave pA_2 values of 7.98, 7.17, 7.64, 7.64, and 7.35, respectively. The slopes of the Schild plots were not significantly different from unity, respectively (Table 3). The antagonists in Table 3 are arranged in order of their pA_2 values found in MSA, with prazosin having the greatest affinity and domperidone having the least.

Antagonism of phenylephrine responses in rat aorta in vitro

Phenylephrine produced concentration-dependent contractions of rat aorta ($pD_2=7.33\pm0.04$, $n=9$) with a greater potency than that seen in the mesenteric small arteries ($pD_2=6.24$, see above). The PE concentration–response curves were markedly right-shifted by prazosin (Fig. 3b and Table 3). Risperidone antagonized the PE-concentration–response curves in rat aorta with high affinity (pA_2 value, 8.36) and no depression of the maximum response at the higher concentration (Fig. 4b, Table 3). Sertindole produced rightward shifts of the concentration–response curves to PE (Fig. 4e), and gave a Schild slope that was greater than unity (1.99, Table 3). Clozapine and haloperidol antagonized PE responses in rat aorta with the same pA_2 values (7.3) but different Schild slopes (Table 3).

We performed Schild analysis for ziprasidone on rat aorta using six different concentration of ziprasidone (Fig. 5e). As ziprasidone gave similar rightward shifts of the PE-concentration–response curves at concentrations 3×10^{-7} and 5×10^{-7} M and very small rightward shift for 10^{-7} M (Fig. 5e), we exposed the vessels with higher concentrations of ziprasidone (10^{-6}, 3×10^{-6}, and 10^{-5} M), and based on these, a low pA_2 value was calculated (6.93) with a Schild slope that was not significantly different from unity (Table 3). Calculated pA_2 value for domperidone was 6.11, with significant depression in maximum response at 10^{-5} M but a Schild slope not significantly different from unity (Fig. 3e and Table 3).

There was no rightward shift of the PE-concentration–response curves in the presence of 10^{-6} M aripiprazole. From the rightward shifts at two higher concentrations (3×10^{-6} and 10^{-5} M, Fig. 5b) pA_2 value equal to 5.96 was calculated. For olanzapine, pA_2 values equal to 6.37 was calculated with a Schild slope that was not significantly different from unity (Table 3).

Comparison of tilt test potencies and pA_2 values in MSA and aorta

The calculated pA_2 values for MSA and aorta were similar for prazosin, risperidone, haloperidol, and clozapine. Markedly lower pA_2 values were, however, seen in aorta vs. MSA for sertindole (pA_2 6.31 vs. 8.78) and to a lesser extent for domperidone, olanzapine, and ziprasidone (pA_2 6.11, 6.37, and 6.93 vs. 6.99, 7.35, and 7.98, respectively). Lowest affinity in aorta was found for aripiprazole, which

Table 1 Mean of ΔAUC_{0-60} and mean of plasma concentration (Cp) for control (HPβC) and drug-treated groups

Compound	Dose (mg/kg, i.v.)	Mean AUC_{0-60} ± SEM (mmHg)	Number of animals		Mean Cp ± SEM (ng/ml)	Number of animals
Control	–	−18.6±71.6	5		– ± –	–
Prazosin**	0.0011	272.7±135.1	5	ns	BLQ ± BLQ	2
	0.0022	217.3±61.1	5	ns	BLQ ± BLQ	2
	0.0044	647.3±163.1	5	ns	1.0±N/A	1
	0.022	923.6±140.9	5	**	4.3±0.4	2
	0.044	1321.1±241.2	5	***	9.7±0.3	2
Risperidone***	0.01	88.4±105.9	5	ns	7.4±1.0	5
	0.03	415.5±120.1	5	ns	20.9±3.9	3
	0.1	835.3±309.2	5	ns	80.7±4.7	3
	0.3	1176.0±154.5	5	*	159.5±37.5	2
	1	1821.3±238.8	5	***	529.8±54.9	4
Sertindole***	0.1	74.1±43.2	5	ns	11.9±1.1	5
	0.2	308.9±125.5	5	ns	19.5±1.4	5
	0.3	701.1±264.4	5	ns	50.1±12.4	5
	1	884.0±215.4	5	*	97.2±17.9	5
	2	863.0±160.8	5	*	261.6±33.6	5
	5	1068.8±166.6	5	**	517.0±50.7	5
Ziprasidone**	0.01	−1.9±72.97	5	ns	5.0±0.5	5
	0.1	639.4±384.7	5	ns	53.4±3.5	2
	0.3	1369.2±143.3	5	*	177.0±15.0	2
	1	1711.1±251.4	5	**	706.0±25.2	3
Clozapine**	0.1	−16.0±68.7	5	ns	16.8±1.3	2
	0.3	387.3±69.1	5	ns	53.0±11.3	2
	1	921.1±514.0	4	ns	184.5±4.5	2
	2	1256.0±116.5	3	ns	292.0±18.6	3
	3	1931.2±124.7	3	**	559.7±67.4	3
Haloperidol[+]	0.3	190.8±173.8	5	N/A	31.0±7.2	2
	1	305.7±197.5	5	N/A	123.5±2.5	2
	3	553.0±365.7	5	N/A	274.0±19.3	3
	10	1014.9±233.6	5	N/A	691.0±5.0	2
Olanzapine*	0.01	12.2±34.2	2	ns	3.2±0.5	2
	0.3	703.6±330.5	4	ns	59.4±11.9	4
	1	1445.9±242.6	4	*	289.5±19.1	4
	3	1462.2±478.1	3	*	740.3±13.6	3
Aripiprazole*	1	−26.9±88.67	5	ns	121.0±19.0	2
	3	274.5±216.2	5	ns	270.0±23.0	3
	10	588.2±217.6	5	*	947.0±83.0	2
	30	214.0±162.5	4	ns	4100.0±152.9	4
Domperidone, ns	0.3	72.2±60.1	5	N/A	66.7±9.1	5
	1	212.8±109.6	5	N/A	253.8±26.2	5
	3	95.1±84.1	5	N/A	772.4±122.1	5
	10	55.4±43.4	2	N/A	2970.0±28.3	2

Data represent the mean ± SEM. Nonparametric test Kruskal–Wallis was used to determine the significance of the overall dosing level.
ns not significant, *N/A* not applicable (no overall significance was found by Dunn's test), *BLQ* below of quantification
*$P<0.05$, significance of differences at each dosing level compared to vehicle by Dunn's test
**$P<0.01$, significance of differences at each dosing level compared to vehicle by Dunn's test
***$P<0.001$, significance of differences at each dosing level compared to vehicle by Dunn's test
[+] $P=0.078$

was also considerably lower than in MSA (pA_2 5.96 vs.7.17, Table 3). As shown in Fig. 6, the potencies of the antipsychotic drugs in the tilt test correlated with the pA_2 values in MSA ($r^2=0.69$, $P=0.01$) but not with the pA_2 values in the aorta ($P=0.21$)

Discussion

The present study appears to be the first where the in vivo potency of a wide range of clinically available typical and atypical antipsychotic drugs in an animal model of

Table 2 The rank number of drugs' potency to cause orthostatic hypotension on the tilt setup

Rank number	Compound	Dose (mg/kg, i.v.)	Mean Cp ± SEM ng/ml
	Prazosin	0.022	4.3±0.4
1	Sertindole	1	97.2±17.9
2	Risperidone	0.3	159.5±37.5
3	Ziprasidone	0.3	177.0±15.0
4	Olanzapine	1	289.5±19.1
5	Clozapine	3	559.7±67.4
6	Haloperidol	10	691.0±5.0
7	Domperidone[a]	10	2970.0±28.3
8	Aripiprazole[a]	30	4100.0±152.9

[a] No dose-dependent effect and no significant effect at highest dose were found. For each compound, the plasma concentration (*C*p) of the first dose having a significant effect from the vehicle has been used to generate the rank number.

orthostatic hypotension has been compared with the functional affinity of these drugs for α_1-AR in separate vascular subtype models in the same species. Eight antipsychotic drugs, plus prazosin as a positive control, were evaluated for their orthostatic hypotensive effect in vivo, and their α_{1A}- and α_{1D}-AR antagonist apparent affinities (pA_2) have been determined in vitro in rat mesenteric small arteries (MSA) and rat thoracic aorta, respectively. In the following, we refer to responses of MSA and aorta as α_{1A}-AR and α_{1D}-AR responses, respectively. The results show a good agreement in the rank order of the in vivo potencies and in vitro affinities for α_{1A}-AR but not for α_{1D}-AR (Table 3).

Investigations employing functional, radioligand binding, and molecular methods have demonstrated the existence of a heterogeneous population of α_1-AR subtypes throughout the vascular system (Kenny et al. 1995; Hussain and Marshall 1997; Docherty 1998; Hrometz et al. 1999). Although the messenger RNA (mRNA) encoding the three α_1-AR subtypes is expressed in many arteries (Piascik and Perez 2001), Marti et al. (2005) found in a molecular and functional study on MSA and rat aorta that the α_{1A} subtype is the dominant subtype in MSA (with 73% of mRNA level) compared with 79% of mRNA level for the α_{1D} subtype in the rat aorta. A major functional role of α_{1A} in MSA has also been proposed by other authors (Ipsen et al. 1997; Stam et al. 1999), whereas several lines of evidence show that the α_{1D}-subtype is the main functional α_1-AR subtype in rat aorta (Hussain and Marshall 1997; Hrometz et al. 1999; Gisbert et al. 2003). Although there are some functional studies on spleen and liver indicating the presence of α_{1B}-AR in these tissues (Sleight et al. 1993; Eltze 1996), as yet there is little direct evidence for the role of the α_{1B}-AR as a mediator of contractile function in blood vessels (Daly et al. 2002). This subtype has only been identified at a low level (1.7–11.1%) of mRNA in peripheral vessels (Marti et al. 2005), confirming previous observations of the lack of α_{1B}-AR in the vasculature (Piascik and Perez 2001).

It is well known that peripheral vasodilators, specifically α_1-AR blockers, such as prazosin and terazosin, have the potential to cause orthostatic hypotension (Andros et al. 1996; Poon and Braun 2005). Consistent with this, in the present study, we found that prazosin had a high potency to cause orthostatic hypotension in our animal model, as well as a high apparent affinity of prazosin for α_1-AR in both MSA and rat aorta (pA_2 9.5 and 10.1, respectively), in agreement with previous studies (Kenny et al. 1995; Hussain and Marshall 1997; Testa et al. 1997; Stam et al. 1999). Antipsychotic drugs also cause blockade of α_1-AR (Schotte et al. 1996; Ipsen et al. 1997; Richelson and Souder 2000; Wadenberg et al. 2000; Schmidt et al. 2001) and also cause postural hypotension; for example, postural hypotension was seen in 77% of the people receiving

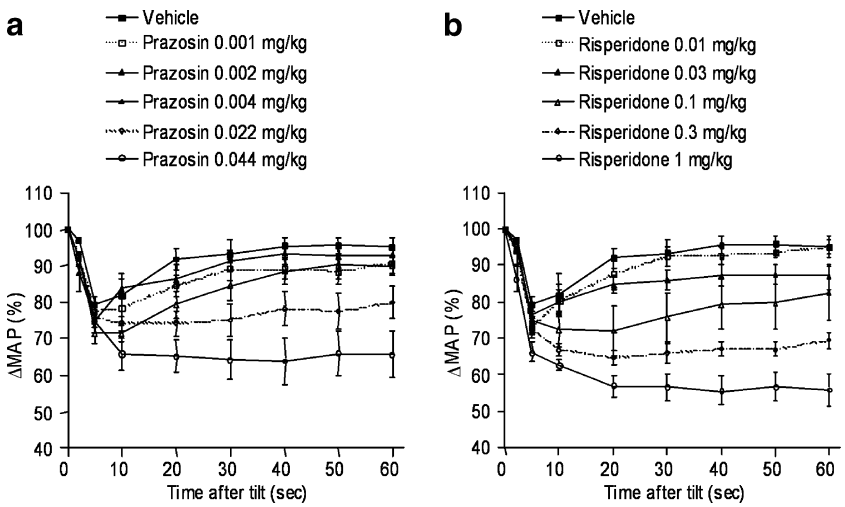

Fig. 2 Effect of **a** prazosin and **b** risperidone on tilt-induced blood pressure response in the anesthetized rats. Mean arterial blood pressure (*MAP*) was taken immediately before tilt (as 0 s) and 5, 10, 20, 30, 40, 50, and 60 s after the start of tilt. Values are given as percentage values compared to baseline values (100%). Changes from the baseline in MAP value before tilt (ΔMAP) were plotted against time after the start of tilt. Each point shows the mean ± SEM of five rats

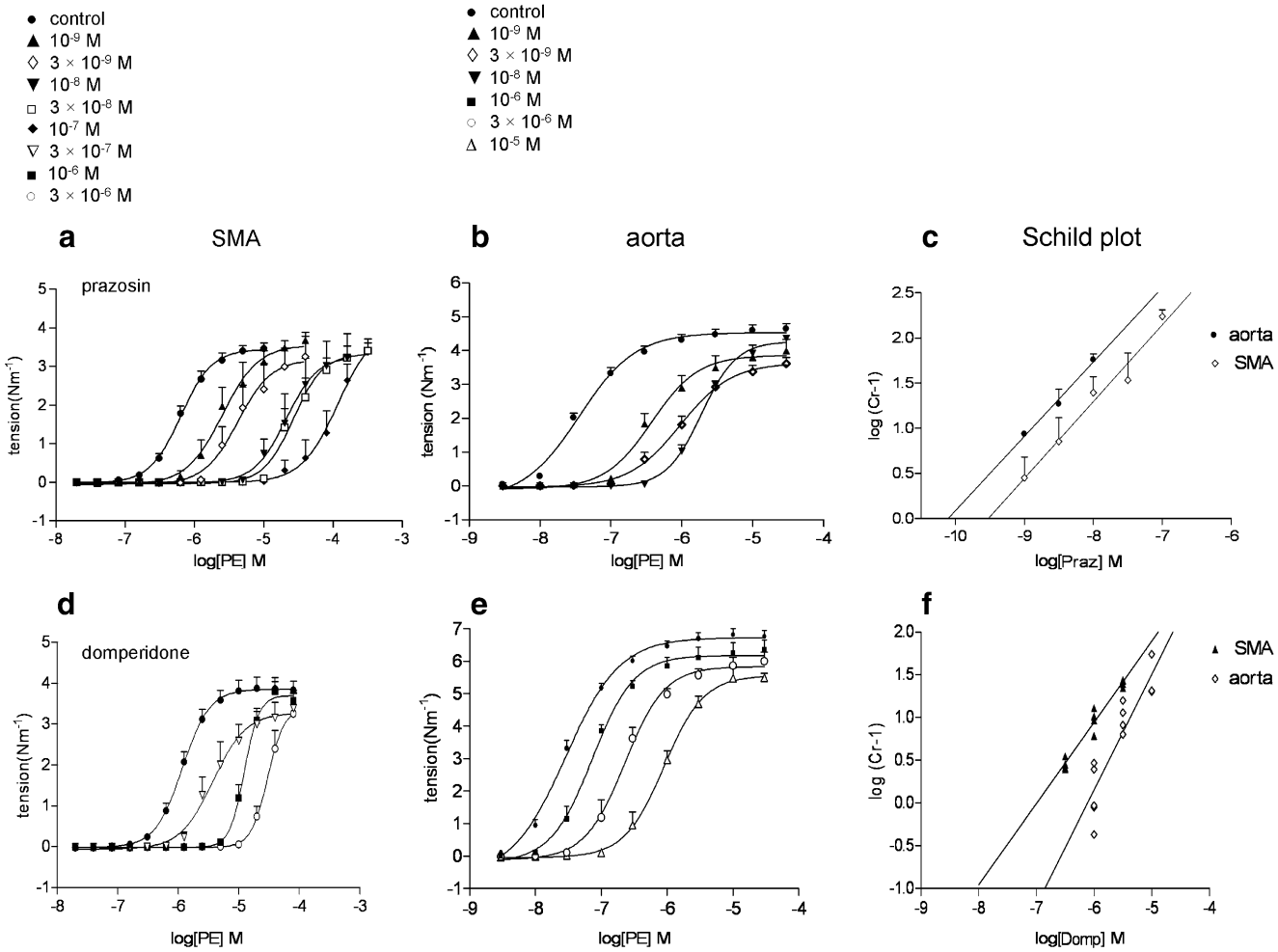

Fig. 3 Phenylephrine concentration–response curves in the presence of prazosin (**a** and **b**) and domperidone (**d** and **e**) on rat endothelial-denuded mesenteric small arteries (**a**, **d**) and rat aorta (**b**, **e**). **c**, **f** show corresponding Schild plots comparing the Schild lines for small mesenteric arteries (*MSA*) and aorta. Each *symbol* represents the mean, and the *vertical lines* show the SEM of at least four separate experiments. For other details, see Table 3

antipsychotic drugs versus 15% receiving placebo (Silver et al. 1990). The side effect of postural hypotension with antipsychotic drugs is thus believed to be mediated by their α_1-AR antagonist affinity (Casey 1996, 1997).

Among the eight antipsychotic drugs investigated in this study, there was a remarkable agreement (Table 3) in the rank orders of potency as regards the induction of orthostatic hypotension and the apparent affinity of the drugs for α_{1A}-AR (as determined in MSA). Thus, risperidone and sertindole had the highest potency concerning orthostatic hypotension and apparent affinity for α_{1A}-AR, in contrast to aripiprazole and domperidone, which show the lowest potencies and affinities in these models. On the other hand, the rank order of apparent affinity for α_{1D}-AR (as determined in aorta) showed little correlation with the rank order of the other two assays (Table 3). Thus, for example, the pA_2 values for both risperidone and sertindole for the α_{1A}-AR were high (pA_2=8.92 and 8.78, respectively), but their affinity for α_{1D}-AR was very different (pA_2=8.36 and 6.31, respectively).

Richelson and Sounder (2000) showed that both risperidone and sertindole had high affinity for α_1-AR using radioligand binding assay and post-morten normal human brain tissue, but the subtypes involved were not investigated. In subtype studies, a high affinity of risperidone for α_{1A}-AR has been found in isolated rat vas deferens (Eltze 1996), although this was not the case for rat hippocampus (Sleight et al. 1993). To our knowledge, there are no data on risperidone affinity for α_{1D}-AR, but low (Eltze 1996) and high (Sleight et al. 1993) affinity for α_{1B}-AR has been reported in guinea pig/mouse spleen and rat hippocampus, respectively. As regards sertindole, the present data confirm previous data from our laboratory, showing that this drug is approximately 300-fold selective for α_{1A}-AR compared to α_{1D}-AR; indeed, the high Schild slope seen here in the aorta experiments (1.99) suggests that sertindole has little

Table 3 Schild analysis of the effect of prazosin, risperidone, sertindole, ziprasidone, clozapine, haloperidol, olanzapine aripiprazole, and domperidone on phenylephrine-concentration–response curves in endothelium-denuded rat small mesenteric artery and rat aorta

Drug	R_{msa} (α_{1A}-AR)			R_{aorta} (α_{1D}-AR)			Rank order in in vivo test[a]
	pA_2	Slope	n	pA_2	Slope	n	
Prazosin	9.52	0.85±0.13	21	10.1	0.82±0.14	12	
Risperidone	8.92	0.86±0.13	12	8.36	0.99±0.21	16	2
Sertindole	8.78	1.24±0.14	12	6.31	1.99±0.21[b]	12	1
Ziprasidone	7.98	1.08±0.18	12	6.93	0.99±0.11	13	3
Clozapine	7.64	1.22±0.10	12	7.39	1.09±0.17	12	5
Haloperidol	7.64	1.11±0.16	12	7.36	0.81±0.12	12	6
Olanzapine	7.35	1.19±0.15	12	6.37	1.22±0.25	12	4
Aripiprazole	7.17	0.98±0.08	12	5.96	1.09±0.47	8	8
Domperidone	6.99	0.95±0.06	13	6.11	1.35±0.19	13	7

Data are calculated pA_2 values, slope of Schild regression line (±SEM) and (n) number of vessels (one vessel per animal).
[a] From Table 2
[b] Slope significantly different from unity

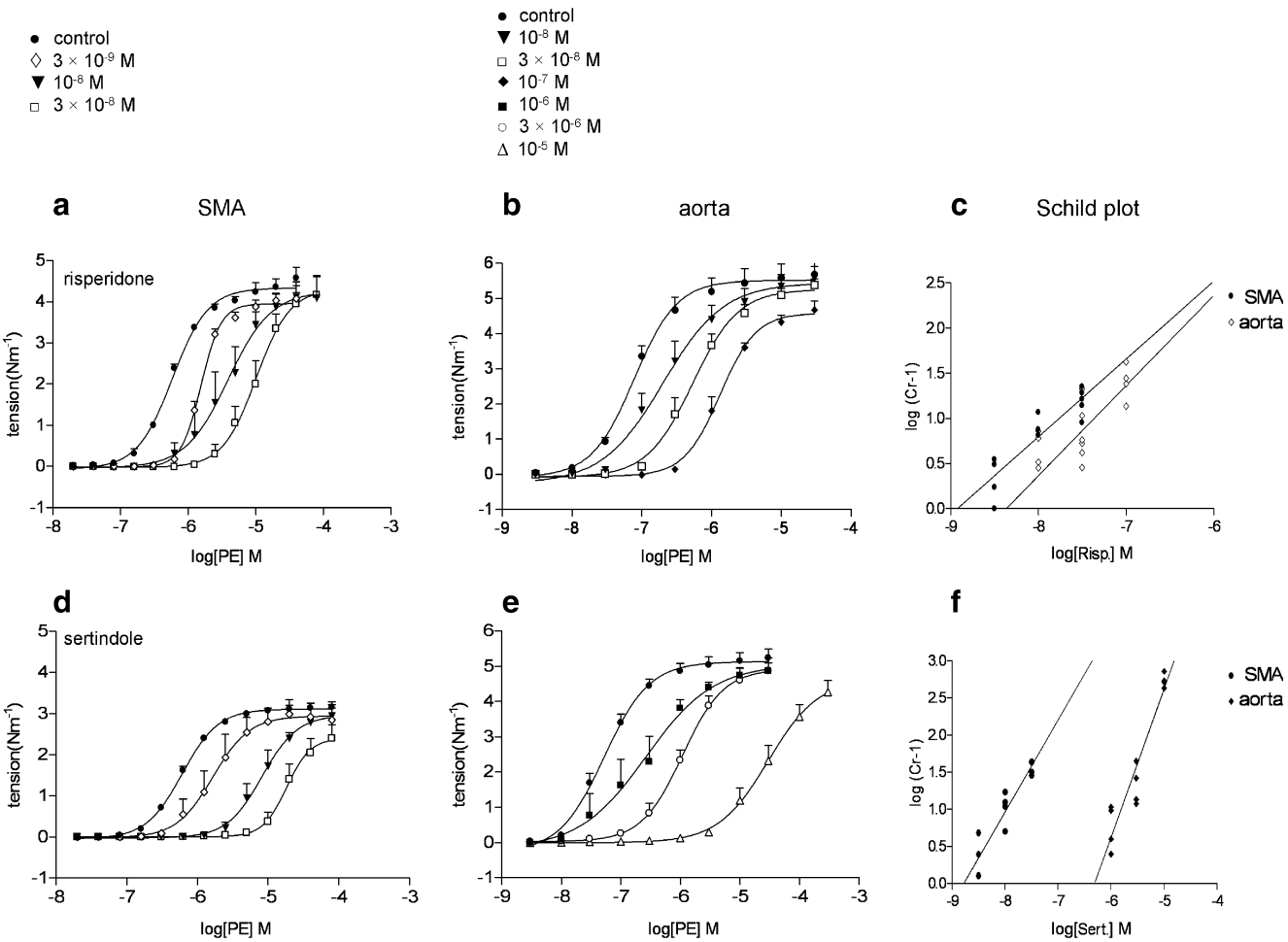

Fig. 4 Phenylephrine-concentration–response curves in the presence of risperidone (**a** and **b**) and sertindole (**d** and **e**) on rat endothelial-denuded mesenteric small arteries (**a**, **d**) and rat aorta (**b**, **e**). **c**, **f** show corresponding Schild plots comparing the Schild lines for small mesenteric arteries (*MSA*) and aorta. Each *symbol* represents the mean, and the *vertical lines* show the SEM of at least four separate experiments. For characteristics, see Table 3

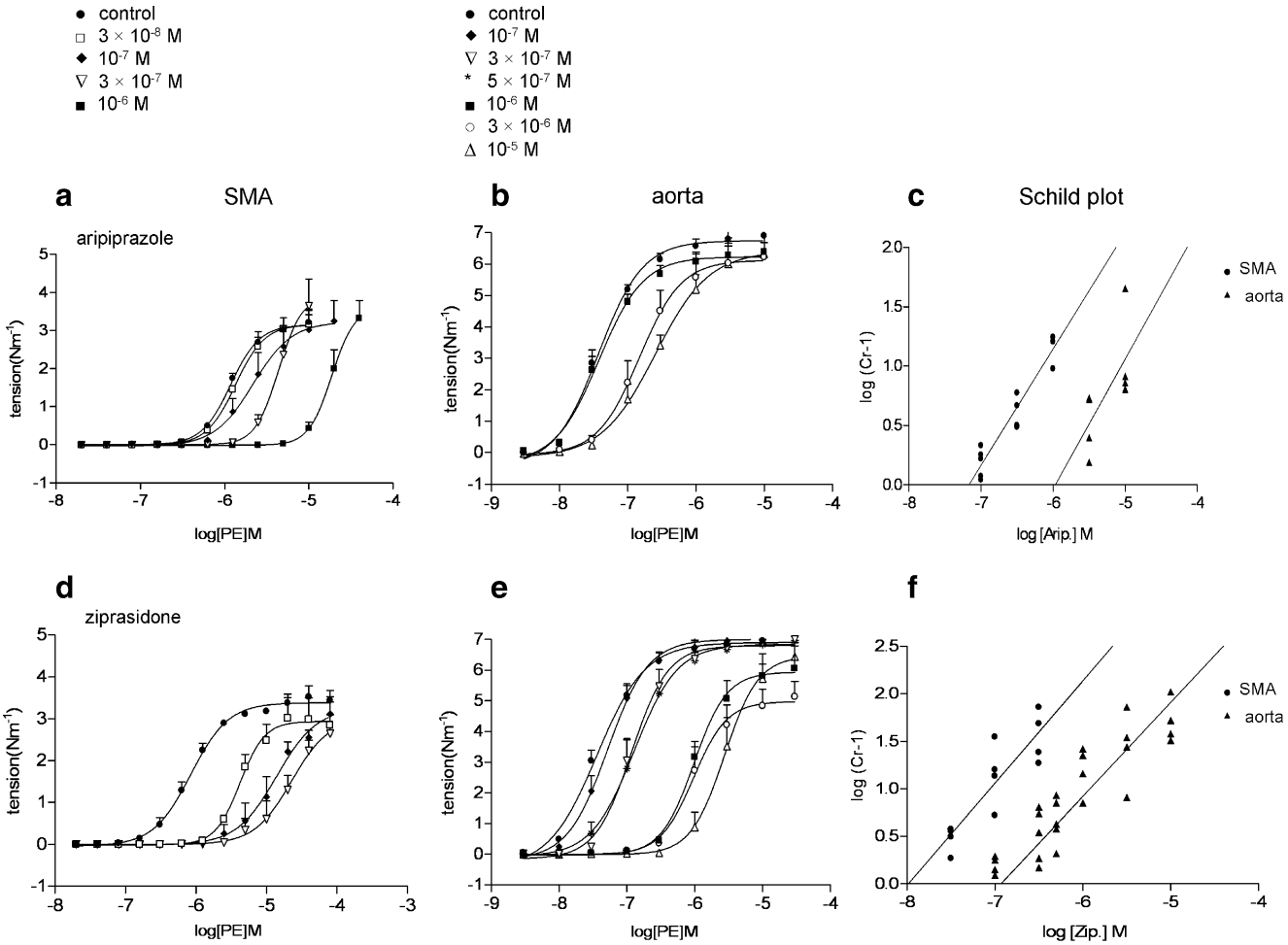

Fig. 5 Phenylephrine concentration–response curves in the presence of aripiprazole (**a** and **b)** and ziprasidone (**d** and **e**) on rat endothelial-denuded mesenteric small arteries (**a**, **d**) and rat aorta (**b**, **e**). **c** and **f** show corresponding Schild plots comparing the Schild lines for mesenteric small arteries (*MSA*) and aorta. Each *symbol* represents the mean, and the *vertical lines* show the SEM of at least four separate experiments. For characteristics, see Table 3

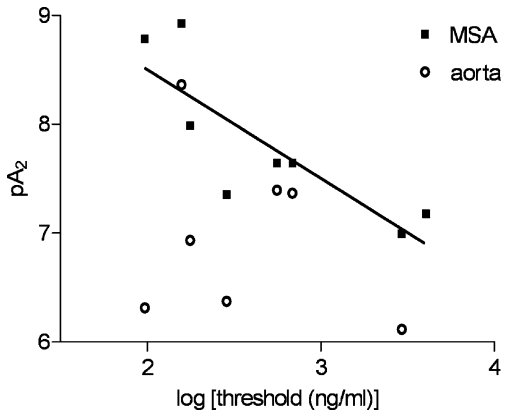

Fig. 6 Comparison of pA_2 values for the investigated antipsychotic drugs determined in mesenteric small arteries (*MSA*) and in aorta with potencies of these drugs in the tilt test (expressed as log [threshold dose]). The data are taken from Tables 2 and 3. Significant correlation was seen for MSA (r^2=0.69, p=0.01, regression line). No correlation was seen for aorta

functional affinity for the α_{1D}-AR. The significance of the low affinity for α_{1D}-AR is not known. The similarity between studies on MSA with and without endothelium confirms that the action of the tested compounds (risperidone and sertindole) is being mediated through effects on the vascular smooth muscle.

Consistent with the high α_{1A}-AR affinity of risperidone and sertindole, and the high potency of these drugs in the tilt test, the incidence of dizziness in patients taking sertindole (Sramek et al. 1997) and risperidone (Barnes and McPhillips 1999) appears to be quite high. For risperidone, the high affinity of risperidone for α_1-AR compared to the low affinity for dopamine D_2 receptors can explain the high risk (48%) of orthostatic hypotension (Poon and Braun 2005). In a case report study, postural hypotension, tachycardia, and syncope have been reported in a patient taking a relatively small overdose of risperidone (Kopala et al. 1998).

Aripiprazole is the first atypical antipsychotic that has potent partial agonist activity at dopamine D_2 and 5-HT1A receptors (Burris et al. 2002; Jordan et al. 2002). In the

present in vivo investigation, no significant effects were found at the highest doses of aripiprazole (Table 2). The pA_2 value for aripiprazole on α_{1A}-AR (7.17) was also relatively low, which is in concordance with the lack of reported orthostatic hypotension in clinical studies (Keck and McElroy 2003), a potential benefit of this drug.

Clinical studies have confirmed that domperidone, as a D_2-antagonist that does not cross the blood–brain barrier, is an effective treatment for preventing early orthostatic hypotension in Parkinson's patients under dopamine agonist therapy (Lang et al. 1990; Sigurdardottir et al. 2001). Such orthostatic hypotension is often found with initiation of dopamine agonist therapy, particularly in Parkinson's disease, and is thought to be caused by venous and arterial dilation through inhibition of the sympathetic nervous system (Kujawa et al. 2000). Our finding of a low potency of domperidone for orthostatic hypotension in the tilt model and a relatively low affinity of domperidone on MSA (pA_2= 6.99) is consistent with the relatively low incidence of orthostatic hypotension when used as a peripheral dopamine antagonist (Lopes et al. 1988).

The relatively low affinity of olanzapine for both investigated α_1-AR subtypes in the present study compared with ziprasidone is in agreement with the study of Schmidt et al. (2001). It was therefore unexpected that olanzapine showed a relatively high potency in the tilt test, and the reason for this discrepancy is not clear. Clinically, olanzapine has a low orthostatic effect (Beasley et al. 1997), but this is thought to be due to the relatively high affinity of olanzapine for dopamine D_2 receptors compared to its affinity for α_1-AR (Schmidt et al. 2001). Radioligand binding studies with ziprasidone by Schmidt et al. (2001) also identified a lower affinity of ziprasidone for human α_1-AR compared to its dopamine D_2 receptors, suggesting that also ziprasidone may have a lower potential to produce orthostatic hypotension in the clinic, but clinical data are lacking.

The anomalous Schild analysis for ziprasidone on rat aorta was unexpected. Here, despite repeated tests, a large gap between phenylephrine concentration–response curves at 5×10^{-7} and 10^{-6} M ziprasidone with depression of the maximum responses at higher concentrations compared to small right shifts without depression in maximum responses by lower concentrations 10^{-7}, 3×10^{-7}, and 5×10^{-7} M of ziprasidone. This behaviour of ziprasidone might be due to partial agonist activity at α_{1D}-AR, but this possibility is not supported by our finding that the Schild slope was unity; thus, further experiments are required to elucidate this anomaly.

The similar potencies in the tilt test for clozapine and haloperidol, and the similar pA_2 values for α_{1A}-AR found in the present investigation are consistent with the similar affinity of clozapine and haloperidol for human α_1-AR reported previously (Schmidt et al. 2001). Clinical data on the orthostatic effects of clozapine are limited, but there are several reports that these are found in some patients (Tuunainen et al. 2002). The findings of the present study are concerned with the acute effects of the drugs investigated. It is, however, well known that the orthostatic hypotensive action of antipsychotics is strongest at the start of treatment and that the effect diminishes over the following days and weeks. The reason for this tolerability is not clear (Stanniland and Taylor 2000). The present study should therefore be considered as providing information that may be relevant for the initial stages of antipsychotic treatment. On this basis, the ability of the antipsychotic drugs, at the higher doses, to prevent recovery of blood pressure during the tilt test (Fig. 2) is consistent with the drug-induced orthostatic hypotension being mediated through the peripheral vascular adrenoceptors. However, as with the exception of domperidone, all the drugs pass the blood–brain barrier, a central contribution to their action cannot be entirely excluded.

In summary, for most of the antipsychotics investigated in the present study, there was a good correlation between the in vivo potency to induce orthostatic hypotension and the affinity for α_{1A}-AR, except olanzapine, which showed slightly higher in vivo potency than expected from the in vitro affinity results. No obvious correlation was found between in vivo effects and affinity toward α_{1D}-AR. Therefore, based on the present comparative functional study, we conclude that α_{1A}-AR are mainly responsible for the orthostatic hypotensive effect of treatment of the rats. Whether this is also the case in man remains to be determined.

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