059P α_1-ADRENOCEPTOR AFFINITY OF ANTIPSYCHOTIC DRUGS

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The therapeutic action of antipsychotic drugs in the treatment of schizophrenia is attributed to their central dopamine antagonist effect (Strange, 2001), but they also have effects on other receptors such as α_1-adrenoceptors in the blood vessels (Buckley et al, 2000). Therefore, a common side effect is orthostatic hypotension, which is probably correlated to their peripheral vascular actions. Here we have determined the α_1-adrenoceptor affinity of some antipsychotic drugs (sertindole, risperidone, clozapine, and ziprasidone) in rat small mesenteric arteries (mainly α_{1A}-adrenoceptors) and rat aorta (mainly α_{1D}-adrenoceptors) as well as prazosin as a positive control.

Male Wistar rats (300-350 g) were killed by cervical dislocation. Small mesenteric arteries (l_{100}=200–300 μm) and thoracic aorta (approx. 2 mm) were mounted as ring preparation on a wire myograph containing physiological salt solution aerated with 5% CO_2 in air at 37°C. After checking viability of vessels, endothelial integrity was assessed using acetylcholine (10^{-5} M, mesenteric; $3*10^{-6}$ M, aorta). The endothelium was removed and viability rechecked. Cumulative concentration response curves were constructed to phenylephrine (PE: 0.02 μM to 640 μM, mesenteric; 3 nM to 30 μM, aorta) in absence and presence of the antipsychotics (30 min incubation). Appropriate vehicle controls and blockers of neuronal and extraneuronal uptake of noradrenaline, β and α_2-adrenoceptors (cocaine, corticosterone 21-acetate, propranolol and yohimbine, respectively) were used throughout. The EC_{50} values in the presence and absence of antipsychotics were used to determine the concentration-ratio (CR). pA_2 values were calculated by Schild analysis.

Table 1 shows the results. For prazosin, risperidone and clozapine pA_2-values were similar for mesenteric arteries and aorta, suggesting antagonism of both α_{1A}- and α_{1D}-adrenoceptors. Sertindole had high affinity for α_{1A}-adrenoceptors, but little affinity for α_{1D}-adrenoceptors. Ziprasidone had lower affinity for α_{1A}-adrenoceptors, and little affinity for α_{1D}-adrenoceptors (for aorta, CR ≅ 1.0 for ziprasidone 1 μM to 10 μM).

	R_{msa}			R_{aorta}		
compound	pA_2	slope	n	pA_2	slope	n
prazosin	9.52	0.85±0.13	21	10.1	0.82±0.14	12
sertindole	8.78	1.24±0.14	12	6.31	1.99±0.21*	12
risperidone	8.92	0.86±0.13	12	8.36	0.99±0.21	16
clozapine	7.64	1.22±0.1	12	7.39	1.09±0.17	12
ziprasidone	7.98	1.08±0.18	12	nc	0.19±0.14*	13

Table 1. Schild analysis of the effect of prazosin, sertindole, risperidone, clozapine, and ziprasidone on phenylephrine concentration-response curves in endothelium-denuded rat small mesentric artery (R_{msa}) and rat aorta. * Slope significantly different from unity; nc, not calculated.

In summary, these results suggest that sertindole and ziprasidone have low affinity for α_{1D} and selectivity for α_{1A}-adrencoceptors.

Buckley, N.A. *et al*. (2000) *Drug Safety*, 23, 215-228.
Strange, P.G. (2001) *Pharmacol. Rev.*, 53, 119-133.