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Short communication

In functional experiments, risperidone is selective, not for the B, but for the A subtype of α_1-adrenoceptors

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Abstract

The potency of the antipsychotic drug, risperidone, to antagonize α_{1A}-adrenoceptor-mediated contraction in rat vas deferens and vasoconstriction in rat perfused kidney, and α_{1B}-adrenoceptor-mediated contractions in spleen from guinea-pig and mouse was evaluated and compared to that of α_1-adrenoceptor subtype-discriminating antagonists. Prazosin was found to be unselective; 2-(2,6-dimethoxyphenoxyethyl)aminomethyl-1,4-benzodioxane (WB 4101), 5-methyl-urapidil, indoramin and (+)-niguldipine were confirmed as selective for the α_{1A}-adrenoceptor, whereas spiperone was weakly α_{1B}-selective. Risperidone was equipotent to prazosin at α_{1A}-adrenoceptors in rat vas deferens and kidney. However, at guinea-pig and mouse splenic α_{1B}-adrenoceptors, the affinity values of risperidone were 10-fold lower than those of prazosin. Thus, in functional experiments the presumed high selectivity of risperidone for the B subtype of α_1-adrenoceptors could not be confirmed, the drug instead appears to be moderately selective (10-fold) for the A subtype.

Keywords: α_1-Adrenoceptor, subtypes A and B; Risperidone; Functional experiment

1. Introduction

On the basis of both functional and radioligand binding experiments two α_1-adrenoceptor subtypes, designated α_{1A} and α_{1B}, were initially identified (Morrow and Creese, 1986; Han et al., 1987). Additionally, molecular biological techniques have allowed cloning and expression of three receptors, i.e. α_{1b} (Cotecchia et al., 1988), α_{1c} (Schwinn et al., 1991), and α_{1d} (Lomasney et al., 1991). The current evidence for the relationship between pharmacologically defined (upper case) and cloned (lower case) α_1-adrenoceptors indicates that: (1) the α_{1b} clone corresponds to the α_{1B}-adrenoceptor; (2) the α_{1d} clone seems to represent a novel subtype, i.e. the α_{1D}-adrenoceptor; (3) the α_{1c} clone corresponds to the α_{1A}-adrenoceptor (Bylund et al., 1994; Forray et al., 1994). Various antagonists are now available that are selective for the A versus the B subtype of α_1-adrenoceptors, e.g. 2-(2,6-dimethoxyphenoxyethyl)aminomethyl-1,4-benzodioxane (WB 4101), 5-methyl-urapidil, (+)-niguldipine, indoramin and tamsulosin (Boer et al., 1989; Forray et al., 1994). Some of these antagonists also exhibit higher affinity at α_{1A}- than at α_{1D}-adrenoceptors, i.e. 5-methyl-urapidil, indoramin and (+)-niguldipine (Forray et al., 1994; Blue et al., 1995). Only two compounds have so far been described as α_{1B}-adrenoceptor-selective antagonists, i.e. the antipsychotic drugs, spiperone and risperidone, which exhibit up to 13- and even 120-fold higher binding affinity, respectively, at α_{1B}- than at α_{1A}-adrenoceptors (Michel et al., 1989; Sleight et al., 1993). In addition to this use of subtype-discriminating antagonists, the sensitivity of mainly α_{1A}-adrenoceptor-mediated effects to Ca^{2+} channel blockade and the sensitivity of α_{1B}- and α_{1D}-adrenoceptor-mediated effects to the irreversible antagonist, chloroethylclonidine, have been used to differentiate between the three subtypes of α_1-adrenoceptors in various tissues (Han et al., 1987; for a recent review, see Bylund et al., 1994).

In view of the reported higher B versus A subtype selectivity of risperidone (Sleight et al., 1993) than of spiperone, it was now aimed to assess the selectivity of risperidone in functional experiments with rat vas def-

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erens and rat perfused kidney for determination of antagonist affinity and potency, respectively, at the A subtype (Han et al., 1987; Eltze and Boer, 1992; Ford et al., 1994; Blue et al., 1995). Spleen from guinea-pig was used for assessing affinity at the B subtype of α_1-adrenoceptors (Eltze, 1994). In addition, we performed contraction experiments with mouse spleen, which has characteristics regarding antagonist affinities, resistance to Ca^{2+} channel blockade and sensitivity to chloroethylclonidine identical to those of guinea-pig spleen α_{1B}-adrenoceptors (Eltze, 1995). Most of the antagonist affinities and potencies at α_1-adrenoceptor subtypes in rat vas deferens, rat kidney and guinea-pig spleen used for comparison have been published previously (Eltze and Boer, 1992; Eltze, 1994).

2. Materials and methods

2.1. Affinity and potency of antagonists at α_{1A}-adrenoceptors in rat vas deferens and rat perfused kidney

Experiments were done with cumulatively added (−)-noradrenaline (10^{-7}–3×10^{-5} M in 0.5 log increments) as the agonist to evoke isotonic contractions of rat prostatic vas deferens segments in the absence and presence (20-min equilibration) of antagonists and in the presence of cocaine (10^{-5} M) (Eltze and Boer, 1992). The results were used for calculation of antagonist affinities (pA_2 values).

The potency of antagonists to reverse the vasoconstriction evoked by (−)-noradrenaline (6×10^{-7} M) in constant-pressure (100 cm H_2O) perfused rat kidney was studied using a technique described previously (Eltze and Boer, 1992). Briefly, once the vasoconstriction induced by continuously present (−)-noradrenaline had stabilized, increasing doses of the test drugs (100 μl) were injected within 2 s into the renal inflow tract and the resulting percent reversal of vasoconstriction was recorded. The $-\log ED_{50}$ (mol) values for half-maximal reversal of vasoconstriction were calculated by non-linear regression analysis. For practical reasons, $-\log ED_{50}$ (mol) values instead of time consuming pA_2 values were determined for the antagonists. We have previously shown that there exists an excellent correlation between antagonist potencies ($-\log ED_{50}$ mol) to reverse (−)-noradrenaline-induced vasoconstriction in rat perfused kidney and (i) antagonist affinities (pK_i) for α_{1A}-adrenoceptor binding sites in rat cortical membranes labeled with [^{3}H]prazosin and (ii) their functional affinities (pA_2) at rat vas deferens α_{1A}-adrenoceptors (Eltze and Boer, 1992). Some antagonist data were taken from a previous paper (Eltze and Boer, 1992). Additional experiments with rat vas deferens were done with risperidone and indoramin, and those with rat kidney, with risperidone, prazosin and indoramin.

2.2. Affinity of antagonists at α_{1B}-adrenoceptors in guinea-pig and mouse spleen

Isometric contractions of guinea-pig isolated spleen strips evoked by cumulative administration of (−)-noradrenaline (3×10^{-8}–10^{-4} M in 0.5 log increments) in the absence and presence (30-min equilibration) of test drug were used to evaluate antagonist affinity (pA_2 value) at α_{1B}-adrenoceptors. These experiments were performed as described previously (Eltze, 1994). Similarly, isolated spleen strips prepared from mice (male, 25–30 g) previously anaesthetized by a short exposure to isoflurane (Forene, Abbott) were mounted in 10-ml organ baths. Isometric contractions in response to cumulatively added (−)-noradrenaline (10^{-8}–10^{-4} M in 1.0 log increments) in the presence of 3×10^{-7} M desipramine, 3×10^{-5} M corticosterone and 10^{-6} M propranolol were measured. Antagonist affinities (pA_2

Table 1
Potencies ($-\log ED_{50}$ mol) of antagonists to reverse (−)-noradrenaline-induced vasoconstriction in perfused rat kidney (RK), affinities (pA_2 values) from constrained Schild plots (slope = 1.00) for competitive antagonism at α_{1A}-adrenoceptors in rat vas deferens (RVD) and at α_{1B}-adrenoceptors in guinea-pig spleen (GPS) and mouse spleen (MS)

	RK ($-\log$ mol)	RVD (pA_2)	GPS (pA_2)	MS (pA_2)	Selectivity α_{1A}/α_{1B}
Prazosin	10.35 ± 0.17	8.90 ± 0.13	9.07 ± 0.09	8.98 ± 0.11	0.8–0.9
WB 4101	11.21 ± 0.19	9.56 ± 0.11	7.93 ± 0.05	8.28 ± 0.12	19–43
5-Methyl-urapidil	10.78 ± 0.16	9.10 ± 0.09	6.95 ± 0.17	7.03 ± 0.07	117–141
(+)-Niguldipine	11.38 ± 0.03	– *	6.32 ± 0.11	6.26 ± 0.16	–
Spiperone	9.54 ± 0.10	7.63 ± 0.03	8.05 ± 0.16	8.29 ± 0.19	0.2–0.4
Risperidone	10.29 ± 0.11	9.08 ± 0.11	8.12 ± 0.07	8.06 ± 0.19	9–10
Indoramin	9.97 ± 0.19	8.52 ± 0.09	6.83 ± 0.12	6.69 ± 0.15	49–68

The α_{1A}-adrenoceptor selectivity range was calculated from the antilog of the difference in pA_2 values of the antagonists in rat vas deferens and guinea-pig or mouse spleen. The results are presented as means ± S.E.M. of $n = 4$–7 for rat kidney and $n = 12$–16 for pA_2 determinations in the other tissues. * Not done due to the strong Ca^{2+} channel antagonism of (+)-niguldipine (Boer et al., 1989). All values without risperidone, prazosin and indoramin at α_{1A}-adrenoceptors in rat kidney and rat vas deferens were taken from Eltze and Boer (1992), and Eltze (1994). All values without risperidone and indoramin at α_{1B}-adrenoceptors in guinea-pig spleen were taken from Eltze (1994).

values) at the guinea-pig and mouse spleen α_{1B}-adrenoceptors were calculated as described for the guinea-pig spleen experiments (Eltze, 1994). Most antagonist data on guinea-pig spleen were taken from this paper. Additional experiments on this tissue were done with risperidone and indoramin.

2.3. Drugs

Risperidone (Janssen, Beerse, Belgium), 5-methyl-urapidil, (+)-(*S*)-niguldipine HCl (Byk Gulden), indoramin HCl (Wyeth), spiperone HCl, prazosin HCl, and 2-(2,6-dimethoxyphenoxyethyl)aminomethyl-1,4-benzodioxane HCl (WB 4101), (RBI, Cologne, Germany). All other drugs were purchased from Sigma (Munich, Germany).

3. Results

3.1. Vas deferens and perfused kidney of the rat

Risperidone (10^{-9}–10^{-7} M), equilibrated with rat vas deferens for 20 min, caused a parallel shift to the right of the (−)-noradrenaline concentration-response curve without affecting the maximum response to the agonist, indicating competitive antagonism at α_{1A}-adrenoceptors in this tissue (not shown). The pA_2 value obtained from the constrained Schild plot was 9.08 ($pA_2 = 9.03$ at a slope = 1.05, not significantly different from 1.00, $P > 0.05$). Similarly, indoramin (10^{-8}–3×10^{-7} M) competitively antagonized contractions in response to (−)-noradrenaline in rat vas deferens, yielding a pA_2 value of 8.52 ($pA_2 = 8.38$ at a slope = 1.13, not significantly different from 1.00, $P > 0.05$) (Table 1).

During vasoconstriction evoked in rat perfused kidneys by (−)-noradrenaline (6×10^{-7} M), when there was a stable and reproducible decrease of 75–80% in perfusion flow, injections of increasing doses of risperidone (10^{-11}–10^{-9} mol) caused a dose-dependent and reversible increase in perfusion flow (not shown). The $-\log ED_{50}$ (mol) value for a half-maximal antivasoconstrictor effect for risperidone was 10.29. The $-\log ED_{50}$ (mol) values for the other antagonists investigated with rat perfused kidney were 10.35 for prazosin and 9.97 for indoramin (Table 1). Other antagonist data on rat kidney were taken from a previous paper (Eltze and Boer, 1992).

3.2. Spleen strips from guinea-pig and mouse

In isolated spleen strips from guinea-pigs and mice, risperidone, equilibrated with the tissues for 30 min (3×10^{-9}–10^{-7} M in guinea-pig spleen, 10^{-8}–3×10^{-7} M in mouse spleen), caused competitive antagonism against (−)-noradrenaline-induced smooth muscle contractions (not shown). The pA_2 values obtained from constrained Schild plots amounted to 8.12 in guinea-pig spleen ($pA_2 = 8.15$ at a slope = 0.97, not significantly different from 1.00, $P > 0.05$), and 8.06 in mouse spleen ($pA_2 = 8.12$ at a slope = 0.94, not significantly different from 1.00, $P > 0.05$). Similarly, prazosin (10^{-9}–10^{-7} M), WB 4101 (10^{-8}–3×10^{-7} M), 5-methyl-urapidil (3×10^{-7}–10^{-5} M), indoramin (3×10^{-7}–3×10^{-5} M), (+)-niguldipine (10^{-6} M) and spiperone (10^{-8}–3×10^{-7} M), caused parallel shifts to the right of the (−)-noradrenaline concentration-response curves in mouse spleen, indicating competitive antagonism. Schild plots for all antagonists investigated with this tissue were linear and yielded slopes of regression not significantly different from unity ($P > 0.05$). The pA_2 values obtained for the antagonists are listed in Table 1. There was excellent agreement for antagonist affinities from experiments with mouse spleen and those with guinea-pig spleen. The small but negligible difference in antagonist affinities, not exceeding 0.3 log units (factor of 2.0), could suggest α_1-adrenoceptor identity, i.e. the B subtype, in spleen smooth muscle from both species.

3.3. α_{1A}-/α_{1B}-Adrenoceptor affinity and potency profile of antagonists

Fig. 1 summarizes the results obtained for risperidone and the reference antagonists. Identical antago-

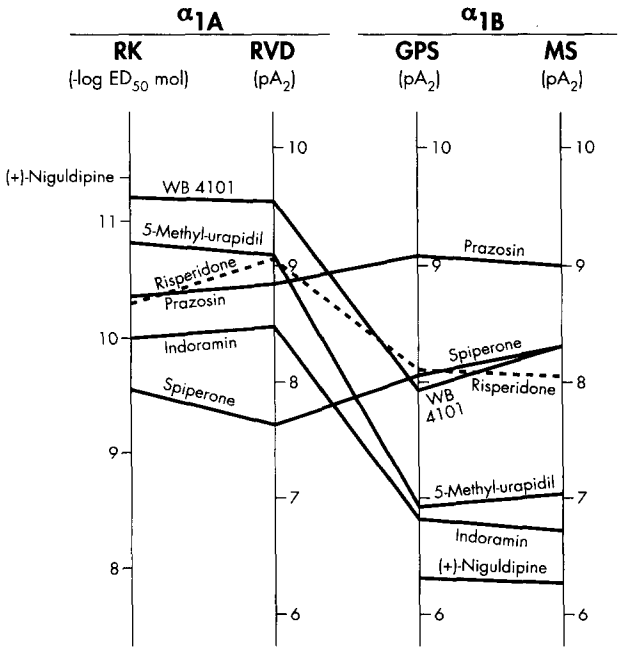

Fig. 1. Diagram comparing the potencies ($-\log ED_{50}$ mol) of risperidone (dashed line) and reference α_1-adrenoceptor antagonists (solid lines) to reverse the (−)-noradrenaline-induced vasoconstriction in perfused rat kidneys (RK) and their affinities (pA_2) at α_{1A}-adrenoceptors in rat vas deferens (RVD) and at α_{1B}-adrenoceptors in guinea-pig spleen (GPS) and mouse spleen (MS).

nist potency and affinity rank order for the drugs were obtained in experiments at α_{1A}-adrenoceptors in rat kidney and rat vas deferens, respectively: (+)-niguldipine (not determined in vas deferens) > WB 4101 > 5-methyl-urapidil > risperidone = prazosin > indoramin > spiperone, which markedly differed from the order observed at α_{1B}-adrenceptors in spleen from both guinea-pig and mouse: prazosin > spiperone = risperidone = WB 4101 > 5-methyl-urapidil = indoramin > (+)-niguldipine. At α_{1A}-adrenoceptors in rat kidney and vas deferens, risperidone showed high affinity and was undistinguishable from prazosin. However, antagonism at α_{1B}-adrenoceptors in spleen from guinea-pig and mouse was 10-fold weaker with risperidone than with prazosin.

4. Discussion

The pharmacological profile of the antipsychotic drug, risperidone, includes interaction with α_1-adrenoceptors, for which the compound has been reported to have an up to 120-fold higher binding affinity at the B subtype ($pK_i = 8.64$ in rat hippocampus, $pK_i = 8.29$ in rat spleen) over the A subtype ($pK_i = 6.55$ in rat hippocampus) (Sleight et al., 1993), whereas no data on its affinity at α_{1D}-adrenoceptors are known. In the present study, we have tried to replicate these findings for the presumed α_{1B}-adrenoceptor selectivity of risperidone by using functional experiments, i.e. vas deferens and perfused kidney of the rat for the A subtype (Han et al., 1987; Eltze and Boer, 1992; Blue et al., 1995), and spleen from guinea-pig and mouse for the B subtype of α_1-adrenoceptors (Eltze, 1994, 1995). We have previously shown that the binding affinities of a number of antagonists at rat cortical α_{1A}-adrenoceptors correlate highly significantly with their potencies to antagonize contraction in rat vas deferens and to reverse vasoconstriction in rat kidneys evoked by (−)-noradrenaline, making both tissues reliable functional assay material for investigating the A subtype of α_1-adrenoceptors (Eltze and Boer, 1992; Ford et al., 1994; Blue et al., 1995).

Although all existing subtypes of α_1-adrenoceptors have been found to be expressed in rat vas deferens, functional studies on this tissue originally performed by Han et al. (1987) demonstrated α_{1A}-adrenoceptors to be the predominant subtype involved in contraction. The affinities of a number of subtype-discriminating antagonists and the resistance to chloroethylclonidine of contraction typically display an α_{1A}-adrenoceptor profile and exclude α_{1B}- or α_{1D}-adrenoceptors as participants in contraction of this tissue (Eltze and Boer, 1992; Bylund et al., 1994; Ford et al., 1994). Particularly, the relatively high affinity values obtained for 5-methyl-urapidil and indoramin in rat vas deferens ($pA_2 = 9.10$ and 8.52, respectively) are consistent with their affinities at cloned α_{1a}-adrenoceptors ($pK_i = 8.7$ and 8.4, respectively; Forray et al., 1994) but differ from the respective values at native α_{1B}-adrenoceptors in mouse and guinea-pig spleen ($pA_2 = 6.9$–7.0 and 6.7–6.8, respectively) and at cloned α_{1b}-adrenoceptors ($pK_i = 6.8$ and 7.4, respectively; Forray et al., 1994). This also holds true for the affinities of these antagonists at cloned α_{1d}-adrenoceptors ($pK_i = 7.9$ and 6.7, respectively; Forray et al., 1994).

On the other hand, the affinity characteristics of antagonists to inhibit smooth muscle contraction in guinea-pig spleen closely resemble the characteristics at α_{1B}-adrenoceptors from rat liver, but differ clearly from those at the A subtype in rat vas deferens and rat cortex (Eltze, 1994). A further functional assay for the B subtype we used was the isolated mouse spleen (Eltze, 1995). The sensitivity of contractions of this tissue to the α_{1B}-adrenoceptor-inactivating agent, chloroethylclonidine (6×10^{-5} M), the total resistance of contractions to Ca^{2+} channel blockade by (±)-isradipine (10^{-7} M) and the affinity profile of subtype-discriminating antagonists, e.g. the relatively low affinities of 5-methyl-urapidil, indoramin and (+)-niguldipine ($pA_2 = 7.03$, 6.69 and 6.26, respectively; this paper), show spleen from mice, like that of the rat (Han et al., 1987), rabbit (Schwinn et al., 1991) and guinea-pig (Eltze, 1994), to have the B subtype of α_1-adrenoceptor.

These reliable functional methods confirmed the reference antagonists WB 4101, 5-methyl-urapidil, indoramin and (+)-niguldipine as selective for α_{1A}-adrenoceptors in rat vas deferens and kidney, as opposed to α_{1B}-adrenoceptors in guinea-pig and mouse spleen ($\alpha_{1A} > \alpha_{1B}$), whereas prazosin was unselective in these tissues ($\alpha_{1A} = \alpha_{1B}$). In contrast to spiperone, which shows an at least 3- to 5-fold selectivity for guinea-pig and mouse spleen α_{1B}-adrenoceptors ($pA_2 = 8.05$ and 8.29, respectively) over rat vas deferens α_{1A}-adrenoceptors ($pA_2 = 7.63$), risperidone shows an inverse selectivity in these tissues ($\alpha_{1A} > \alpha_{1B}$). Risperidone thereby qualitatively resembles WB 4101, but with a minor (10-fold) selectivity for the A subtype as calculated from the difference in affinity at rat vas deferens α_{1A}-adrenoceptors ($pA_2 = 9.08$) and at guinea-pig or mouse spleen α_{1B}-adrenoceptors ($pA_2 = 8.12$ and 8.06, respectively).

In summary, whereas these functional experiments confirmed the selectivity of WB 4101, 5-methyl-urapidil, indoramin and (+)-niguldipine for the A subtype and weak selectivity of spiperone for the B subtype, they showed risperidone to be moderately selective (10-fold) for the A subtype of α_1-adrenoceptors. The reason for the discrepancy between the antagonist affinities and selectivity of risperidone found in the present functional experiments and those reported from

binding studies (Sleight et al., 1993) still remains unclear. As a result, the possible usefulness of risperidone for α_1-adrenoceptor discrimination, at least for the A and B subtype, appears limited.

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