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Affinity of the Miotic Drug, Dapiprazole, at α_1-Adrenoceptor Subtypes A, B and D

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Abstract

The functional affinities of the α_1-adrenoceptor antagonist, dapiprazole, currently being used to reverse diagnostic pupillary dilation, were determined at subtype A in rat vas deferens, at subtype B in guinea-pig spleen and at subtype D in rat aorta and compared with various α_1-adrenoceptor subtype-discriminating antagonists.

Dapiprazole had relatively high affinity both at rat vas deferens α_{1A}-adrenoceptors ($pA_2 = 7{\cdot}93$) and at rat aortic α_{1D}-adrenoceptors ($pA_2 = 8{\cdot}26$), whereas its affinity at guinea-pig splenic α_{1B}-adrenoceptors ($pA_2 = 7{\cdot}13$) was lower. The reference antagonists, 5-methylurapidil and the 5-methylurapidil/flesinoxan hybrid, B8805-033 ((±)-1,3,5-trimethyl-6[[3[4(2(2,3-dihydro-2-hydroxymethyl)-1,4-benzodioxin-5-yl)-1-piperazinyl]propyl]-amino]2,4(1*H*,3*H*)-pyrimidinedione), were 40- and 1500-fold selective for the A subtype, whereas spiperone and BMY 7378 (8-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspiro[4.5]decane-7,9-dione diHCl) were confirmed as selective for the B and D subtypes of α_1-adrenoceptors, respectively.

Thus, in functional experiments dapiprazole seems to be moderately selective (approximately 10-fold) for the A and D over the B subtype of α_1-adrenoceptors; the possible therapeutic consequence of this is discussed.

α_1-Adrenoceptors comprise a heterogeneous family (Minneman & Esbenshade 1994). Molecular biological techniques have provided evidence for the existence of at least three genes encoding α_{1a}-, α_{1b}- and α_{1d}-adrenoceptors (with lowercase letters) that are expressed in distinct parts of the brain and body (for recent reviews, see Bylund et al 1994; Hieble et al 1995) and that correspond to the pharmacologically defined native α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors (with uppercase letters) (Morrow & Creese 1986; Han et al 1987; Cotecchia et al 1988; Lomasney et al 1991; Schwinn et al 1991; Forray et al 1994). Each of these subtypes has been observed to have a distinct expression pattern in various tissues in man (Weinberg et al 1994, Faure et al 1995).

Dapiprazole (3-{2-[4-(2-methylphenyl)-1-piperazinyl]ethyl}-5,6,7,8-tetrahydro-1,2,4-triazolo-[4,3-a]pyridine HCl; Fig. 1), currently being used as eye-drops to reverse the diagnostic mydriasis produced by the α_1-adrenergic agent, phenylephrine, or the antimuscarinic drug, tropicamide, is thought to initiate this effect by α_1-adrenoceptor blockade (Doughty & Lyle 1992). Functional and binding studies have demonstrated that dapiprazole, in the concentration range 10^{-8} to 10^{-7} M, inhibits noradrenaline-evoked contraction of rat vas deferens (Lisciani et al 1982) and binds to α_1-adrenoceptors in rabbit iris (Valeri et al 1986) and various brain regions of the rat (Valeri et al 1988), however, studies exploring its affinity for the subtypes A, B and D of α_1-adrenoceptors are lacking. This might be of particular importance, because the hypothesis had been advanced (Alessandri et al 1992) of a heterogeneous population of at least two different α_1-adrenoceptors located in the iris dilator muscle in man, one being activated by endogenous noradrenaline and the other by phenylephrine, and which differ in their sensitivity to Ca^{2+} entry blockade. Although characterization of these subtypes and their functions still awaits elucidation, recent in-vitro data suggest that the relevant α_1-adrenoceptor mediating phenylephrine-induced contraction of the iris dilator muscle in man has similarity to the subtype L (Ishikawa et al 1996), which is distinct from the commonly known subtypes A, B and D (Muramatsu et al 1990a). Therefore, the ability of agents such as dapiprazole to initiate the reversal of mydriasis by blockade of α_1-adrenoceptors raises the question of their possible selectivity for existing α_1-adrenoceptor subtypes.

The aim of this study was to determine the functional affinity of dapiprazole at different α_1-adrenoceptors by using rat vas deferens for subtype A (Han et al 1987; Eltze & Boer 1992; Ford et al 1994), spleen from guinea-pig for subtype B (Eltze 1994) and rat thoracic aorta for subtype D (Kenny et al 1995; Testa et al 1995; Eltze 1996). Antagonists which are selective for the A subtype of α_1-adrenoceptor, rather than the B and D subtypes, namely 5-methylurapidil (Gross et al 1988) and its newly developed flesinoxa hybrid, B8805-033 (Eltze et al 1996), as well as spiperone (Michel et al 1989) and BMY 7378 (Goetz et al 1995) known to be selective for α_{1B}- and α_{1D}-adrenoceptors, respectively, were used for comparison. Affinities of the reference antagonists at α_1-adrenoceptor subtypes in these tissues have previously been published (Eltze & Boer 1992; Eltze 1994, 1996; Eltze et al 1996).

Materials and Methods

Drugs

Dapiprazole HCl (extracted from the lyophilized powder of Remydrial) was from Winzer (Germany). 5-Methylurapidil, B8805-033 ((±)-1,3,5-trimethyl-6[[3[4((2,3-dihydro-2-hydroxymethyl)-1,4-benzodioxin-5-yl)-1-piperazinyl]propyl]-amino]-2,4(1*H*,3*H*)-pyrimidinedione) was from Byk Gulden. Spiperone HCl, prazosin HCl, and BMY 7378 (8-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspiro[4.5]decane-7,9-dione diHCl) were from RBI (Cologne, Germany). All other drugs were purchased from Sigma (Munich, Germany).

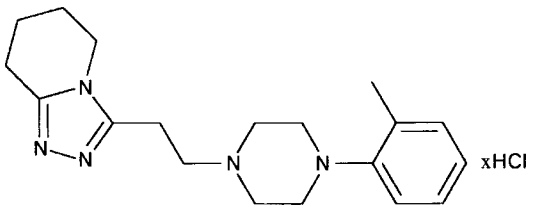

FIG. 1. The chemical structure of dapiprazole.

Affinity of antagonists at α_{1A}-adrenoceptors in rat vas deferens
Experiments 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 for calculation of antagonist affinities (pA_2 values) were performed as described in detail elsewhere (Eltze & Boer 1992).

Affinity of antagonists at α_{1B}-adrenoceptors in guinea-pig spleen
Isometric contractions of guinea-pig isolated splenic strips evoked by cumulative administration of noradrenaline (10^{-7}–3×10^{-5} M in 0·5-log increments) in the absence and presence (30 min equilibration) of test drug for determination of antagonist affinity (pA_2 value) at α_{1B}-adrenoceptors were performed as previously described (Eltze 1994).

Affinity of antagonists at α_{1D}-adrenoceptors in rat thoracic aorta
Isometric contractions in response to cumulatively added noradrenaline (10^{-8}–3×10^{-6} M in 0·5-log increments) in the absence and presence of antagonists (30 min equilibration) on the rat isolated thoracic aorta were performed as previously described (Eltze & Boer 1992).

Antagonist affinities
At least four agonist concentration–response curves were recorded until contraction of the tissues was reproducible. The antagonist-induced shifts were related to the final control curve and determined for each individual preparation. Schild plots were constructed to estimate the pA_2 value and the slope β of the regression line from each experimental series, which generally comprised at least four different antagonist concentrations (Arunlakshana & Schild 1959). The pA_2 values quoted in Table 1 were calculated from Schild plots in which the slopes of the regression lines were constrained to 1·00. When the slope of the Schild plot differed significantly ($P < 0.05$) from unity, pA_2 values determined from constrained regression lines ($\beta = 1.00$) should be regarded as approximations.

Results

Rat vas deferens: α_{1A}-adrenoceptors
Dapiprazole (10^{-8}–10^{-7} M), equilibrated with the rat vas deferens for 20 min, shifted noradrenaline concentration–response curves to the right indicating mainly competitive antagonism at α_{1A}-adrenoceptors in this tissue, but concomitantly reduced the maximum contraction to the agonist by 8 to 22% (Fig. 2). Concentrations of dapiprazole greater than 10^{-7} M, which gradually reduced maximum contractions of noradrenaline by more than 25% (not shown) were not used for the regression analysis. This possibly resulted from Ca^{2+} entry blockade and a non-specific smooth muscle depressant activity described for dapiprazole (Lograno et al 1987). In particular, Ca^{2+}-channel blockers preferentially inhibit noradrenaline-evoked contraction of rat vas deferens after α_{1A}-adrenoceptor stimulation (Han et al 1987; Eltze & Boer 1992). The pA_2 value obtained from the constrained three-point Schild plot was 7·93 ($pA_2 = 7.91$ at a slope = 1·02, not significantly different from 1·00, $P > 0.05$; Fig. 3). Affinities for the reference antagonists 5-methylurapidil, prazosin, B8805-033, spiperone and BMY 7378, previously determined in this tissue (Eltze 1994, 1996; Eltze et al 1996) are also included in Table 1.

Guinea-pig spleen: α_{1B}-adrenoceptors
In isolated splenic strips from guinea-pig dapiprazole (10^{-7}–3×10^{-6} M), equilibrated with the tissues for 30 min, caused parallel shifts to the right of the noradrenaline concentration-response curves and, at the highest concentration tested (3×10^{-6} M), slightly reduced the maximum response to the agonist; this possibly occurred because of its known non-specific smooth muscle relaxant effect (Lograno et al 1987) (Fig. 2). The pA_2 value obtained from constrained Schild plot was to

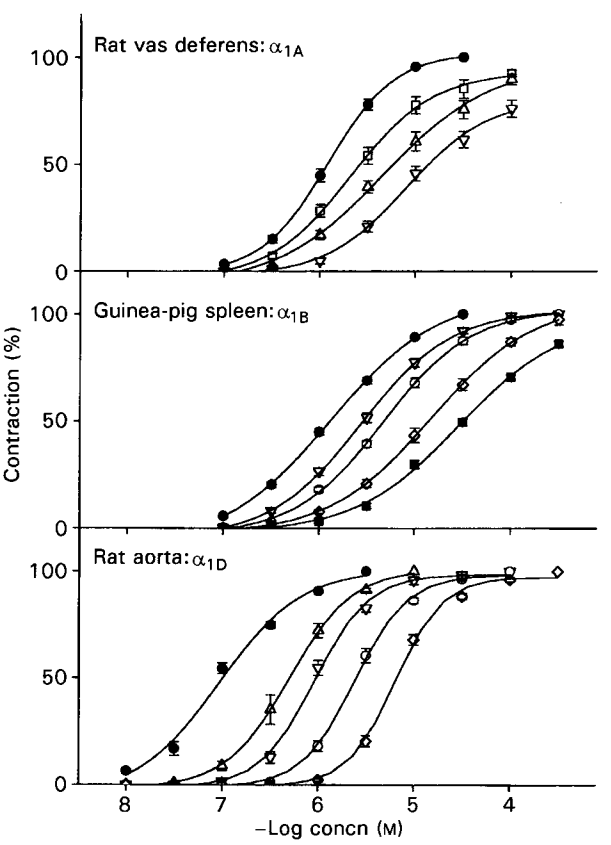

FIG. 2. Representative concentration–response curves of the contraction evoked by noradrenaline in isolated rat vas deferens, in guinea-pig spleen and in rat aorta in the absence (●) or presence of dapiprazole (□, 10^{-8} M; △, 3×10^{-8} M; ▽, 10^{-7} M; ○, 3×10^{-7} M; ◇, 10^{-6} M; ■, 3×10^{-6} M) equilibrated with the tissues for 20–30 min. Values are means ± s.e.m. of n = 8–12 results for the control and n = 6–8 results in the presence of each concentration of dapiprazole.

7·13 ($pA_2 = 7·17$ at a slope = 0·97, not significantly different from 1·00, $P > 0·05$; Fig. 3). The affinities of reference antagonists are also listed in Table 1.

Rat thoracic aorta: α_{1D}-adrenoceptors

Dapiprazole (3×10^{-8}–10^{-6} M), equilibrated with the rat aorta for 30 min, competitively antagonized α_{1D}-adrenoceptor-mediated contraction to noradrenaline in this tissue without affecting the maximum response of the agonist (Fig. 2). A pA_2 value of 8·26 was calculated from the constrained Schild plot ($pA_2 = 8·19$ at a slope = 1·07, not significantly different from 1·00, $P > 0·05$; Fig. 3). The pA_2 values obtained for the reference antagonists previously determined in rat aorta (Eltze & Boer 1992; Eltze 1994, 1996; Eltze et al 1996) are also listed in Table 1.

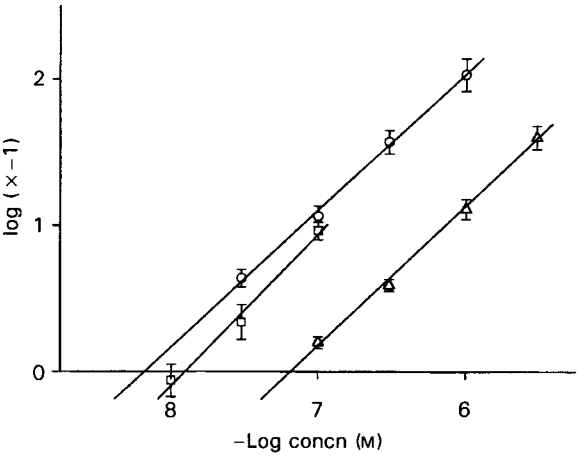

FIG. 3. Schild plots for dapiprazole inhibition of noradrenaline-evoked contraction of the isolated rat vas deferens (□), guinea-pig spleen (△) and rat aorta (○). Values are means ± s.e.m. of n = 9–15 results.

Discussion

α_1-Adrenoceptor blockade appears to be the predominant feature of dapiprazole, marketed as eye-drops for reversing the diagnostic mydriasis induced by phenylephrine, tropicamide or their combination (Lisciani et al 1982; Valeri et al 1986, 1988; Doughty & Lyle 1992); however, nothing is known about the mechanism of its interaction with the subtypes A, B and D of α_1-adrenoceptors. By using functional in-vitro methods, the reference antagonists, 5-methylurapidil and B8805-033, were confirmed as selective for α_{1A}-adrenoceptors in rat vas deferens as opposed to α_{1B}-adrenoceptors in guinea-pig spleen and α_{1D}-adrenoceptors in rat aorta ($\alpha_{1A} > \alpha_{1B} = \alpha_{1D}$), whereas prazosin behaved unselectively in these tissues ($\alpha_{1A} = \alpha_{1B} = \alpha_{1D}$). BMY 7378 had approximately 30-fold greater affinity for α_{1D}- than for either α_{1A}- or α_{1B}-adrenoceptors ($\alpha_{1D} > \alpha_{1A} = \alpha_{1B}$). In contrast with spiperone, which shows slight selectivity for α_{1B}-adrenoceptors over both α_{1A}- and α_{1D}-adrenoceptors ($\alpha_{1B} > \alpha_{1A} = \alpha_{1D}$), dapiprazole shows approximately 10-fold greater affinity for the A or D than for the B subtype of α_1-adrenoceptors ($\alpha_{1A} = \alpha_{1D} > \alpha_{1B}$).

Pupil diameter is an opposing dynamic function of the noradrenergic innervation of the iris dilator muscle producing mydriasis and cholinergic innervation of the iris sphincter muscle producing miosis (Turner 1975; van Alphen 1976; Yoshitomi et al 1985). Little is known about the possible existence of α_1-adrenoceptor subtypes on the iris dilator muscle in man and the mechanisms and response characteristics whereby α_1-adrenoceptor stimulation and blockade result in pupil dilation and contraction, respectively. Initially the hypothesis of at least two different α_1-adrenoceptors located in this tissue had been advanced by using nimodipine, which attenuated mydriasis evoked by conjunctival instillation of tyramine but not that of phenylephrine (Alessandri et al 1992). Because α_2-adrenoceptors, which are generally sensitive to Ca^{2+} entry blockade (van Meel et al 1981), are not detectable on the iris dilator muscle in man (Fanciullacci et al 1988) the possibility of their involvement in the mydriatic effect elicited by tyramine can be excluded; it is most likely that it is based on stimulation of α_{1A}- rather than of α_{1B}- or α_{1D}-adrenoceptors, whereas the nimodipine-resistant mydriatic effect after phenylephrine is more consistent with the characteristics of responses generally observed after α_{1B}- and α_{1D}-adrenoceptor stimulation (Han et al 1987; Minneman 1988; Schwinn et al 1991). If this is true, it could be speculated that α_{1A}-adrenoceptors reside in the synaptic region of neuromuscular junction within the iris dilator muscle where they are primarily activated by neuronal noradrenaline release, whereas α_{1B}- or α_{1D}-adrenoceptors, or both, are located in perisynaptic regions where they can be stimulated pharmacologically by exogenous α_1-adrenoceptor agonists or physiologically by plasma catecholamines, the presence of which has been demonstrated in the vascular system of the rat (Vargas et al 1994; Zhou & Vargas 1996).

Table 1. Affinities (pA_2 values with slopes of regression, β, in parentheses) from constrained Schild plots (slope = 1·00) for dapiprazole and reference antagonists at α_{1A}-adrenoceptors in rat vas deferens, at α_{1B}-adrenoceptors in guinea-pig spleen and at α_{1D}-adrenoceptors in rat aorta.

Antagonist	α_{1A}-Adrenoceptors in rat vas deferens	α_{1B}-Adrenoceptors in guinea-pig spleen	α_{1D}-Adrenoceptors in rat aorta
Dapiprazole	7.93 ± 0.10 (1.02)	7.13 ± 0.09 (0.97)	8.26 ± 0.05 (1.07)
Prazosin	8.90 ± 0.13 (0.91)	9.07 ± 0.09 (0.99)	8.85 ± 0.09 (0.90)
5-Methylurapidil	9.10 ± 0.09 (1.06)	6.95 ± 0.17 (0.91)	7.46 ± 0.05 (0.89)
B8805-033	8.40 ± 0.11 (1.26)*	5.21 ± 0.08 (1.05)	5.24 ± 0.11 (0.85)
Spiperone	7.63 ± 0.03 (0.93)	8.05 ± 0.16 (0.77)*	7.82 ± 0.08 (0.75)*
BMY 7378	6.67 ± 0.15 (0.93)	6.55 ± 0.18 (1.02)	8.15 ± 0.16 (1.00)

The results are presented as means ± s.e.m. of n = 9–15 results for each pA_2 determination in the various tissues. All values for the reference antagonists without dapiprazole were taken from Eltze (1994, 1996), Eltze & Boer (1992) and Eltze et al (1996). *Slope β significantly different from unity ($P < 0·05$).

Most recently, the α_1-adrenoceptor in isolated human iris dilator muscle activated by phenylephrine and blocked by exceptionally high concentrations of prazosin ($pA_2 = 7{\cdot}3$; Ishikawa et al 1996), has been suggested as belonging to a new subtype, designated α_{1L} (Muramatsu et al 1990a). However, the higher affinity of phentolamine ($pA_2 = 7{\cdot}5$) than of 5-methylurapidil ($pA_2 = 6{\cdot}6$) in the iris in man (Ishikawa et al 1996) is also consistent with the affinity difference observed at cloned and expressed α_{1b}-adrenoceptors (average $pK_i = 7{\cdot}4$ compared with 6·9; values taken from Eltze 1996), as they have been shown to exist in iris dilator muscle of the rat (Hill et al 1993) and the rabbit (Takayanagi et al 1992). Presently, the observed characteristics of the differentially initiated and blockable responses in the iris of man in-vivo (Alessandri et al 1992) and in-vitro (Ishikawa et al 1996) are difficult to interpret, but it has been tentatively suggested that α_{1A}-adrenoceptors mediate neuronally induced mydriasis; no conclusion can be made about other α_1-adrenoceptor subtypes (L or B, or both) involved in mydriasis evoked by exogenous agonists until more data for α_1-adrenoceptor subtype-discriminating antagonists, which should differentially block each mydriatic response, are available. Preliminary experiments on rabbit aorta, which is considered to be endowed with α_{1L}-adrenoceptors (Muramatsu et al 1990b), showed dapiprazole to have relatively low affinity ($pA_2 = 7{\cdot}04$; Eltze, unpublished) comparable with that determined at α_{1B}-adrenoceptors in guinea-pig spleen ($pA_2 = 7{\cdot}13$).

Whether the resulting functional receptor selectivity profile observed for dapiprazole ($\alpha_{1A} = \alpha_{1D} > \alpha_{1B} = \alpha_{1L}$) has any therapeutic consequence in respect of preferential blockade of one or several α_1-adrenoceptor subtype(s) specifically involved in mydriasis (A, and L or B, or both) is unclear. However, by considering the applied dose of dapiprazole generally needed for reversing mydriasis (1 to 4 drops of a 0·5% solution, i.e. a concentration of $1{\cdot}5 \times 10^{-2}$ M; Doughty & Lyle 1992) and the relatively narrow concentration range which blocks all existing α_1-adrenoceptor subtypes (approximately a factor of 10), this seems rather unlikely.

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References

Alessandri, M., Pietrini, U., Bandini, E. B., Beatrice, S., Fanciullacci, M. (1992) Action of nimodipine on sympathomimetic mydriasis in humans. Clin. Neuropharmacol. 15: 120–128

Arunlakshana, O., Schild, H. O. (1959) Some quantitative uses of drug antagonists. Br. J. Pharmacol. 14: 48–58

Bylund, D. B., Eickenberg, D. C., Hieble, J. P., Langer, S. Z., Lefkowitz, R. J., Minneman, K. P., Molinoff, P. B., Ruffolo, R. R., Trendelenburg, U. (1994) International Union of Pharmacology: nomenclature of adrenoceptors IV. Pharmacol. Rev. 46: 121–136

Cotecchia, S., Schwinn, D. A., Randall, R. R., Lefkowitz, R. J., Caron, M. G., Kobilka, B. K. (1988) Molecular cloning and expression of the cDNA for the hamster α_1-adrenergic receptor. Proc. Natl Acad. Sci. USA 85: 7159–7163

Doughty, M. C., Lyle, W. M. (1992) A review of the clinical pharmacokinetics of pilocarpine, moxisylate (thymoxamine), and dapiprazole in the reversal of diagnostic pupillary dilation. Optometry Vision Sci. 69: 358–368

Eltze, M. (1994) Functional characterization of the α_1-adrenoceptor subtype mediating contraction of guinea-pig spleen. Eur. J. Pharmacol. 260: 211–220

Eltze, M. (1996) Functional evidence for an $_{1B}$-adrenoceptor mediating contraction of the mouse spleen. Eur. J. Pharmacol. 311: 187–198

Eltze, M., Boer, R. (1992) The adrenoceptor agonist, SDZ NVI 085, discriminates between α_{1A}- and α_{1B}-adrenoceptor subtypes in vas deferens, kidney and aorta of the rat. Eur. J. Pharmacol. 224: 125–136

Eltze, M., Boer, R., Sanders, K. H., Prüsse, W., Ulrich, W. R. (1996) B8805-033: an extremely alpha$_{1A}$-adrenoceptor-selective antagonist. Naunyn Schmiedebergs Arch. Pharmacol. 354 (Suppl.): R9

Fanciullacci, M., Pietrini, U., Fusco, B. M., Alessandri, M., Marabini, S., Sicuteri, F. (1988) Does anisocoria by clonidine reflect a central sympathetic dysfunction in cluster headache? Clin. Neuropharmacol. 11: 56–62

Faure, C., Gouhier, C., Langer, S. Z., Graham, D. (1995) Quantification of α_1-adrenoceptor subtypes in human tissues by competitive RT-PCR analysis. Biochem. Biophys. Res. Commun. 213: 935–943

Ford, A. P. D. W., Williams, T. J., Blue, D. R., Clarke, D. E. (1994) α_1-Adrenoceptor classification: sharpening Occam's razor. Trends Pharmacol. Sci. 15: 167–170

Forray, C., Bard, J. A., Wetzel, J. M., Chiu, G., Shapiro, E., Tang, R., Lepor, H., Hartig, P. R., Weinshank, R. L., Branchek, T. A., Gluchowski, C. (1994) The α_1-adrenergic receptor that mediates smooth muscle contraction in human prostate has the pharmacological properties of the cloned α_{1c} subtype. Mol. Pharmacol. 45: 703–708

Goetz, A. S., King, H. K., Ward, S. D. C., True, T. A., Rimele, T. J., Saussy, D. L. (1995) BMY 7378 is a selective antagonist of the D subtype of α_1-adrenoceptors. Eur. J. Pharmacol. 272: R5

Gross, G., Hanft, G., Rugevics, C. (1988) 5-Methylurapidil discriminates between subtypes of the α_1-adrenoceptor. Eur. J. Pharmacol. 151: 333–335

Han, C. H., Abel, P. W., Minneman, K. P. (1987) α_1-Adrenoceptor subtypes linked to different mechanisms for increasing intracellular Ca^{2+} in smooth muscle. Nature (London) 329: 333–335

Hieble, J. P., Bylund, D. B., Clarke, D. E., Eickenburg, D. C., Langer, S. Z., Lefkowitz, R. J., Minneman, K. P., Ruffolo, R. R. (1995) International Union of Pharmacology, X. Recommendations for nomenclature of α_1-adrenoceptors. Pharmacol. Rev. 47: 267–270

Hill, C. E., Klemm, M., Edwards, F. R., Hirst, G. D. (1993) Sympathetic transmission to the dilator muscle of the rat iris. J. Auton. Nerv. Syst. 45: 107–123

Ishikawa, H., Miller, D. D., Patil, P. N. (1996) Comparison of postjunctional α-adrenoceptors in iris dilator muscle of humans, and albino and pigmented rabbits. Naunyn Schmiedebergs Arch. Pharmacol. 354: 765–772

Kenny, B. A., Chalmers, D. H., Philpott, P. C., Naylor, A. M. (1995) Characterization of an α_{1D}-adrenoceptor mediating the contractile response of rat aorta to noradrenaline. Br. J. Pharmacol. 115: 981–986

Lisciani, R., Baldini, A., Silvestrini, B. (1982) General pharmacological properties of dapiprazole, a potent psychotropic agent. Arzneim. Forsch. 32: 674–678

Lograno, M. D., Reibaldi, A., Camerino, D. C. (1987) Effects of dapiprazole on contractile responses of guinea-pig isolated ileum. Pharmacol. Res. Comm. 19: 209–221

Lomasney, J. W., Cotecchia, S., Lorenz, W., Leung, W. Y., Schwinn, D. A., Yang-Feng, T. L., Brownstein, M., Lefkowitz, R. J., Caron, M. G. (1991) Molecular cloning and expression of the cDNA for the α_{1A}-adrenergic receptor, the gene for which is located on chromosome 5. J. Biol. Chem. 266: 6365–6369

Michel, A. D., Loury, D. N., Whiting, R. L. (1989) Identification of a single α_1-adrenoceptor corresponding to the α_1-subtype in rat submaxillary gland. Br. J. Pharmacol. 98: 883–889

Minneman, K. P. (1988) α_1-Adrenergic receptor subtypes, inositol phosphates, and sources of Ca^{2+}. Pharmacol. Rev. 40: 87–119

Minneman, K. P., Esbenshade, T. A. (1994) α_1-Adrenergic receptor subtypes. Annu. Rev. Pharmacol. Toxicol. 34: 117–133

Morrow, A. L., Creese, I. (1986) Characterization of α_1-adrenergic receptor subtypes in rat brain: a reevaluation of [^{3}H]WB 4101 and [^{3}H]prazosin binding. Mol. Pharmacol. 29: 321–330

Muramatsu, I., Ohmura, T., Kigoshi, S., Hashimoto, S., Oshita, M. (1990a) Pharmacological subclassification of α_1-adrenoceptors in vascular smooth muscle. Br. J. Pharmacol. 99: 197–201

Muramatsu, I., Kigoshi, S., Oshita, M. (1990b) Two distinct α_1-adrenoceptor subtypes involved in noradrenaline contraction of the rabbit thoracic aorta. Br. J. Pharmacol. 101: 662–666

Schwinn, D. A., Page, S. O., Middleton, J. P., Lorenz, W., Ligget, S. B., Yamamoto, K., Lapetina, E. G., Caron, M. G., Lefkowitz, R. J., Cotecchia, S. (1991) The α_{1C}-adrenergic receptor: characterization of signal transduction pathways and mammalian tissue heterogeneity. Mol. Pharmacol. 40: 619–626

Takayanagi, I., Shiraishi, K., Kokubu, N. (1992) α_{1B}-Adrenoceptor mechanisms in rabbit iris dilator muscle. Jpn J. Pharmacol. 59: 301–305

Testa, R., Distefani, C., Guarneri, L., Poggesi, E., Simonazzi, I., Taddei, C., Leonardi, A. (1995) The α_{1d}-adrenoceptor subtype is involved in the noradrenaline-induced contraction of rat aorta. Life Sci. 57: 159–163

Turner, P. (1975) The human pupil as a model for clinical pharmacological investigation. J. R. Coll. Physicians Lond. 9: 165–171

Valeri, P., Palmery, M., Severini, G., Piccinelli, D., Catanese, B. (1986) Ocular pharmacokinetics of dapiprazole. Pharmacol. Res. Commun. 18: 1093–1105

Valeri, P., Palmery, M., Silvestrini, B. (1988) Binding profile of trazodone and dapiprazole to some brain receptors. Drugs Exp. Clin. Res. 14: 53–58

van Alphen, G. W. H. M. (1976) The adrenergic receptors in the intraocular muscles of the human eye. Invest. Ophthalmol. 15: 502–521

van Meel, J. C. A., de Jonge, A., Kalkman, H. O., Wilfert, B., Timmermans, P. B. M. W. M., van Zwieten, P. A. (1981) Organic and inorganic calcium antagonists reduce vasoconstriction in vivo mediated by postsynaptic alpha$_2$-adrenoceptors. Naunyn Schmiedebergs Arch. Pharmacol. 316: 288–293

Vargas, H. M., Zhou, L., Gorman, A. J. (1994) Role of vascular alpha-1 adrenoceptor subtypes in the pressor response to sympathetic nerve stimulation in the pithed rat. J. Pharmacol. Exp. Ther. 271: 748–754

Weinberg, D. H., Trivedi, P., Tan, C. P., Mitra, S., Perkins-Barrow, A., Borkowski, D., Strader, C. D., Bayne, M. (1994) Cloning, expression and characterization of human α-adrenergic receptors α_{1A}, α_{1B} and α_{1C}. Biochem. Biophys. Res. Commun. 201: 1296–1304

Yoshitomi, T., Ito, Y., Inomata, H. (1985) Adrenergic excitatory and cholinergic inhibitory innervations in the human iris dilator. Exp. Eye Res. 40: 453–459

Zhou, L., Vargas, H. M. (1996) Vascular α_{1D}-adrenoceptors have a role in the pressor response to phenylephrine in the pithed rat. Eur. J. Pharmacol. 305: 173–176