This work was supported by a grant from the National Health and Medical Research Council of Australia and this aid is gratefully acknowledged. We would also like to thank Dr Lesley J. Bryan for helpful discussions. A preliminary report on this work was presented to the Australian Physiological and Pharmacological Society (Braun & O'Donnell 1980).

REFERENCES

Anning, E. N., Bryan, L. J., O'Donnell, S. R. (1979) Br. J. Pharmacol. 65: 175–182

Braun, R. A., O'Donnell, S. R. (1980) Proc. Austr. Physiol. Pharmacol. Soc. 11: 40P

Bowman, W. C., Rodger, I. W. (1972) Br. J. Pharmacol. 45: 574–583

Bryan, L. J., O'Donnell, S. R. (1979) Naunyn-Schmiedeberg's Arch. Pharmacol. 307: 235–241

Bryan, L. J., O'Donnell, S. R. (1980a) Ibid. 311: 139–146

Bryan, L. J., O'Donnell, S. R. (1980b) J. Pharmacol. Methods 4: 29–42

Bryan, L. J., O'Donnell, S. R. (1981) Naunyn-Schmiedeberg's Arch. Pharmacol. 315: 249–254

Carney, I., Daly, M. J., Lightowler, J. E., Pickering, R. W. (1971) Arch. Int. Pharmacodyn. 194: 334–345

Corrodi, H., Hillarp, N.-Å., Jonsson, G. (1964) J. Histochem. Cytochem. 12: 582–586

Corrodi, H., Jonsson, G. (1967) Ibid. 15: 65–78

Falck, B. (1962) Acta Physiol. Scand. 56: Suppl. 197, 1–25

Garland, L. G., Marrion, N. V., Martin, G. R. (1981) Naunyn-Schmiedeberg's Arch. Pharmacol., 318: 88–93

Marquardt, D. W. (1963) J. Soc. Ind. Appl. Math. 11: 431–441

Marlin, G. E., Turner, P. (1975) Br. J. Clin. Pharmacol. 2: 41–48

O'Donnell, S. R., Saar, N. (1978) Br. J. Pharmacol. 62: 235–239

O'Donnell, S. R., Wanstall, J. C. (1976) Ibid. 57: 369–373

O'Donnell, S. R., Wanstall, J. C. (1977) Arch Int. Pharmacodyn. 226: 214–223

Shenfield, G. M., Evans, M. E., Paterson, J. W. (1976) Br. J. Clin. Pharmacol. 3: 583–589

Snedecor, G. W., Cochran, W. G. (1980) Statistical Methods, 7th ed. The Iowa State University Press, Iowa, pp. 149–174

J. Pharm. Pharmacol. 1982, 34: 671–673
Communicated April 7, 1982

0022–3573/82/100671–03 $02.50/0

A preferential blocking effect of oxprenolol on α_1-adrenoceptors in the rat

E. VILA, A. BADIA*, F. JANÉ, *Department de Farmacologia i Terapèutica, Facultat de Medicina, Universitat Autònoma de Barcelona, Bellaterra, Barcelona, Spain*

It is now widely accepted that α-adrenoceptors can be subdivided into α_1 and α_2 subtypes (Berthelsen & Pettinger 1977). While α_1-adrenoceptors are located postsynaptically, α_2-adrenoceptors are situated not only at presynaptic nerve terminals (Langer 1977; Starke 1977) but also postsynaptically, at least in the vascular smooth muscle (Docherty et al 1979; Drew & Whiting 1979; Timmermans & Van Zwieten 1980). The β-blocking agent oxprenolol appears to have some α-adrenoceptor antagonist properties (Mazurkiewicz-Kwilecki 1970; Law et al 1978; Vila et al 1978; Roselló et al 1978). We have investigated the effects of oxprenolol on the α-adrenoceptor subtypes in several rat preparations. The in vitro studies were carried out on the field-stimulated vas deferens and the anococcygeus muscle of the rat, and the in vivo study was in the pithed rat.

Methods

The entire vasa deferentia from male Sprague-Dawley rats, 300–325 g, were removed and set up in isolated organ baths containing 20 ml of Krebs solution as modified by Huković (1961). The solution was maintained at 32 ± 0·5°C and gassed with 95% O_2-5% CO_2.

* Correspondence.

Platinum ring electrodes were placed above and below the preparation and continuous field stimulation was by means of an Ealing stimulator (0·1 Hz, 3 ms and 20–30 V). The responses of the preparation against 0·5 g tension were recorded by means of an isotonic transducer on an Omniscribe pen recorder. Xylazine was used as α_2-adrenoceptor agonist (Docherty & McGrath 1980), and when the twitch contractions of the vas became stable, cumulative concentration-response curves of the inhibitory effect of the agonist were obtained. As a full recovery after washout of the agonist was difficult to obtain, one vas deferens was used as a control while in the other the activity of xylazine was evaluated 5 min after the addition of oxprenolol. Only two concentrations of antagonist could be used (3×10^{-5} and 1×10^{-4} mol litre^{-1}), and the pA_2 was determined according to the method described by van Rossum (1963). To rule out effects mediated by β-adrenoceptors, experiments were carried out in presence of 1×10^{-7} mol litre^{-1} of propranolol.

The postsynaptic α_1-adrenergic blocking activity of oxprenolol was evaluated on the isolated anococcygeus muscle as suggested by Doxey et al (1977). The muscle from male Sprague-Dawley rats, 250–300 g, was dissected as described by Gillespie (1972). The tissue was set

up as for the vas deferens. The temperature was 37 ± 0·5 °C. The responses were recorded as before under 0·5 g resting tension. Cumulative concentration-response curves of isotonic contractions were obtained with the α_1-adrenoceptor agonist methoxamine (Kobinger & Pichler 1980). The concentration-response curves as control and in the presence of oxprenolol (3×10^{-6}, 1×10^{-5}, 3×10^{-5} mol litre^{-1} added 5 min before obtaining each curve) were constructed for each preparation and it was possible to calculate the pA_2 and the slopes of Schild plots (Arunlakshana & Schild 1959) of the antagonist in each experiment.

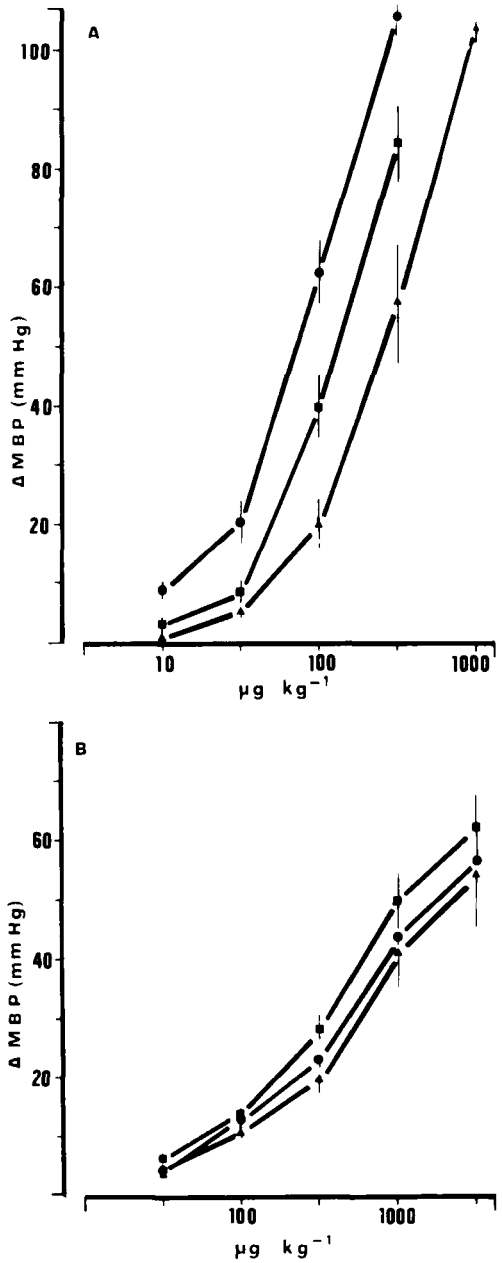

FIG. 1. Effect of oxprenolol on the dose-response curves of methoxamine (A) and xylazine (B) in the pithed rat. (●——●), control; (■——■), after 1 mg kg^{-1} of oxprenolol; (▲——▲) after 3 mg kg^{-1} of oxprenolol. Abscissa: logarithm of drug doses. Ordinate: increase of mean blood pressure. Each point is the mean of six experiments. Vertical bars show standard errors of the mean.

The in vivo experiments were performed on artificially ventilated (60 strokes min^{-1}, 1 ml 100 g^{-1}) pithed Sprague-Dawley rats (300–350 g). Rectal temperature was kept at approximately 37 °C. The left carotid artery was cannulated and the arterial blood pressure was measured by means of a Statham transducer connected on a polygraph (Hewlett-Packard, mod. 7786 A). In some experiments the heart rate was measured by means of a cardiotachometer connected to the arterial pulse. Drugs were injected through a polythene cannula into the right jugular vein. Experiments began after an equilibration period of 15 min. To study the α_1-adrenoceptor activity, control mean blood pressure dose-response curves to methoxamine or after oxprenolol (1–3 mg kg^{-1}), given 5 min before, were obtained. The α_2-blocking activity was determined as the antagonism of the dose-response curves of increases of mean blood pressure elicited by single doses of xylazine. One group of rats was used as control and in two other groups the pressor effects of the agonist were quantified 5 min after the pretreatment with different doses of oxprenolol (1–3 mg kg^{-1}). In all cases, xylazine was used in a random order. In another group of experiments α_1- and β-adrenergic blocking potency were compared by studying the effects of increasing doses of oxprenolol against the rises of mean blood pressure induced by 100 μg kg^{-1} of methoxamine and against the chronotropic responses induced by 0·03 μg kg^{-1} of isoprenaline respectively. In the two sets of experiments the ED50 were determined.

The results obtained were expressed as the mean ± s.e.m., and for comparison between groups Student's *t*-test was used.

Table 1. Mean pA_2 values of oxprenolol on the presynaptic α_2-adrenoceptors in the field stimulated rat vas deferens, and on the postsynaptic α_1-adrenoceptors in the rat anococcygeus muscle.

Agonist	n[a]	pA_2 ± s.e.m.[b]	slope[c] ± s.e.m.
		presynaptic	
Xylazine	6	4·87 ± 0·06	—
		postsynaptic	
Methoxamine	6	6·50 ± 0·01	0·97 ± 0·01

[a] Number of experiments.
[b] Mean and the standard error of the mean.
[c] Slope of Schild plots (Arunlakshana & Schild 1959).

Results

At the concentrations used, oxprenolol in the presence of propranolol did not inhibit the twitch response of the vas deferens. On the other hand, as can be seen in Table 1, the pA_2 value for oxprenolol against methoxamine on the anococcygeus muscle was greater ($P < 0.001$) than the corresponding value against xylazine on the field stimulated vas deferens. From the calculated pA_2, it can be seen that oxprenolol is 46 times more active on the postsynaptic α_1-adrenoceptors.

Methoxamine produces mean blood pressure increases in the pithed rat through the activation of α_1-adrenoceptors (Kobinger & Pichler 1980) while the pressor responses to xylazine are due to stimulation of postsynaptic α_2-adrenoceptors (Docherty & McGrath 1980). Doses of 1 and 3 mg kg^{-1} of oxprenolol shifted the pressor response curve of methoxamine by 1·9 ($P < 0.05$) and 5·2 ($P < 0.02$) fold respectively to the right but those of xylazine were not modified (Fig. 1). On the other hand the ED50 of oxprenolol against the pressor response of methoxamine was 1·98 ± 0·02 mg kg^{-1} while that against the chronotropic response of isoprenaline was 0·026 ± 0·002 mg kg^{-1}, showing that the α_1-adrenergic blocking activity is 1/75th its potency as a β-adrenoceptor blocking agent.

Discussion

All these results suggest that oxprenolol, in addition to its β-adrenergic blocking activity, is an α_1-adrenoceptor antagonist in vitro as well as in vivo. The in vitro pA_2 value for oxprenolol is similar to that found for labetalol, a mixed α- and β-adrenoceptor antagonist, in the guinea-pig mesenteric vein and in the rat vas deferens (Farmer et al 1972). On the other hand, oxprenolol is 50 to 150 times less potent as an α_1-adrenoceptor blocking agent when its pA_2 is compared with that obtained by Horii et al (1974) (pA_2 = 8·2–8·7) as a β-adrenergic blocking agent. Furthermore this difference is of the same order as that obtained in our in vivo experiments. It has clearly been established that blockade of the presynaptic α_2-adrenoceptor results in a loss of the inhibitory feed-back mechanism and enhances the release of the adrenergic neurotransmitter from sympathetic nerve terminals (Langer 1977). The increase in noradrenaline concentration could counteract both the blockade at the cardiac β-adrenoceptors and the antagonism at α-adrenoceptors on vascular smooth muscle. This probably does not occur with oxprenolol because it preferentially antagonizes α_1-adrenoceptors. However, our results cannot explain the increase in the stimulation-induced efflux of [^{3}H]noradrenaline in the presence of oxprenolol in the guinea-pig atria obtained with lower concentrations that those used in our experiments (Majewski et al 1980). These differences may suggest a lack of correspondence between efflux studies, and pharmacological studies that use the end-organ responses for assessing presynaptic α-adrenoceptor effects. Finally, blockade of the postsynaptic α_1-adrenoceptors could explain the reduction in peripheral resistance observed with oxprenolol (Wilson et al 1968) and contribute to its antihypertensive effect (Waal-Manning 1976).

The generous supply of oxprenolol hydrochloride (Ciba-Geigy), xylazine hydrochloride (Bayer), methoxamine hydrochloride (Gayoso-Wellcome) is acknowledged.

REFERENCES

Arunlakshana, O., Schild, O. H. (1959) Br. J. Pharmacol. 14: 48–58

Berthelsen, S., Pettinger, W. A. (1977) Life Sci. 21: 595–606

Docherty, J. R., MacDonald, A., McGrath, J. C. (1979) Br. J. Pharmacol. 77: 421P

Docherty, J. R., McGrath, J. C. (1980) Naunyn-Schmiedeberg's Arch. Pharmacol. 312: 106–116

Doxey, J. C., Smith, C. F. C., Walker, J. M. (1977) Br. J. Pharmacol. 60: 91–96

Drew, G. M., Whiting, S. B. (1979) Ibid. 67: 207–215

Farmer, J. B., Kennedy, I., Levy, G. P., Marshall, R. J. (1972) Ibid. 45: 660–675

Gillespie, J. S. (1972) Ibid. 45: 404–416

Horii, D., Kaweda, T., Takeda, K., Imai, S. (1974) Arzneim-Forsch. 24: 1275–1277

Huković, S. (1961) Br. J. Pharmacol. 16: 188–194

Kobinger, W., Pichler, L. (1980) Eur. J. Pharmacol. 65: 393–402

Majewski, H., McCulloch, M. V., Rand, M. J., Story, D. F. (1980) Br. J. Pharmacol. 71: 435–444

Mazurkiewicz-Kwilecki, I. M. (1970) Eur. J. Pharmacol. 11: 155–162

Langer, S. Z. (1977) Br. J. Pharmacol. 60: 481–497

Law, M., Rand, M. J., Story, D. F. (1978) Clin. Exp. Pharmacol. Physiol. 5: 284

Roselló, M. J., Guinot, C., Jané, F. (1978) Proc. 7th Int. Cong. Pharmacol. Abst. 1414 (Paris)

Starke, K. (1977) Rev. Physiol. Biochem. Pharmacol. 77: 1–24

Timmermans, P. B. M. W. M., Van Zwieten, P. A. (1980) Eur. J. Pharmacol. 63: 199–202

Van Rossum, J. M. (1963) Arch. Int. Pharmacodyn. 143: 299–330

Vila, E., Badia, A., Jané, F. (1978) Proc. 7th Int. Cong. Pharmacol. Abst. 2914 (Paris)

Waal-Manning, H. J. (1976) N.Z. Med. J. 83: 223–226

Wilson, D. F., Watson, O. F., Peel, J. S., Langley, R. B., Turne, A. S. (1968) Ibid. 68: 145–149