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# Ketanserin—a novel antihypertensive drug

P. M. VANHOUTTE*, J. M. VAN NUETEN†, *Department of Physiology and Biophysics, Mayo Clinic, Rochester, Minnesota 55905 U.S.A. and †Department of Pharmacology, Janssen Pharmaceutica, B-2340, Beerse, Belgium*

We read with interest and some surprise the letter to the Editor in the Journal, entitled 'Ketanserin—A Novel Antihypertensive Drug?', by Humphrey et al (1982). We were the first to point out that ketanserin, at higher concentrations, has $\alpha_1$-adrenergic blocking properties and to consider that this may help explain its antihypertensive action in the spontaneously hypertensive rat (Van Nueten et al 1981), Dr Humphrey and colleagues refer only to an abstract by Fozard (1982a) in that regard). We agree with Fozard (1982b), Kalkman et al (1982) and Persson et al (1982) that in the rat, ketanserin may lower blood pressure primarily because of its α-adrenergic blocking properties; we had not done the experiments to rule that out when we reported the basic vascular pharmacology of the compound (Van Nueten et al 1981). However, as we have pointed out (Vanhoutte 1982a,b; Vanhoutte et al 1982), in man the antihypertensive effect of ketanserin is hard to reconcile with $\alpha_1$-adrenergic blockade alone since therapeutic doses of the compound do not shift the pressor dose response curves to phenylephrine (Wenting et al 1982; Zoccali et al 1982). Hence, to suggest that the blood pressure lowering effect of ketanserin in man is related to its major pharmacological action, inhibition of 5-$HT_2$ receptors (whether they involve the direct or amplifying effects of the monoamine; Van Nueten et al 1981, 1982), seems scientifically acceptable.

Dr Humphrey and colleagues summarize published and unpublished work, relating the affinity to 5-$HT_2$-binding sites and the responsiveness to 5-hydroxytryptamine of the rabbit aorta. This only confirms identical correlations obtained in other isolated blood vessels, allowing the conclusion that the 5-hydroxytryptaminergic receptors on these vascular smooth muscle cells can reasonably be subtyped as 5-$HT_2$-binding sites (Peroutka & Snyder 1979; Cohen et al 1981; Van Nueten et al 1981; Leysen et al 1982). Hence, it is not obvious that these receptors should be called 'D-receptors' rather than 5-$HT_2$-receptors (Cohen et al 1981; Van Nueten et al 1981), according to current pharmacological thinking.

Dr Humphrey and colleagues state that cyproheptadine and pizotifen have no notable agonistic activity, quoting unpublished and published observations (Apperley et al 1976, 1980). Agonistic activities of high concentrations of these two compounds, but not of ketanserin, can be demonstrated in the rat jugular vein (Fig. 1), the rat fundus (Van Nueten et al 1982) and in the central nervous system (Colpaert et al 1982; Janssen 1982). Although these occur at relatively high concentrations, the hypertensive blood vessel wall is notably hyperresponsive to vasoconstrictor stimuli, and, in particular, 5-hydroxytryptaminergic agonists and antagonists with agonistic properties (e.g. Vanhoutte 1978, 1982a, b, 1983; Webb 1982). Again, in view of these observations, it seems scientifically acceptable to propose that the apparent absence of agonistic properties, as a rather unique feature among the available 5-hydroxytryptaminergic antagonists, could contribute to the antihypertensive properties of ketanserin.

We agree fully with Dr Humphrey and colleagues that unequivocal evidence demonstrating a role of 5-HT in hypertension in man is not available, and we have said so (Vanhoutte 1982a, b, 1983; Vanhoutte et al 1982). Future experiments will undoubtedly explain exactly why ketanserin lowers blood pressure in the hypertensive subject; why it does so in rats and other animals may have little relevance to the understanding of the etiology of human hypertension. After carefully reviewing all the information available on the animal and human pharmacology of ketanserin, we feel that it is reasonable and proper to propose that its inhibitory effect on vasoconstrictor, as opposed to vasodilator response to 5-HT, and its lack of agonistic properties, play a key role. However, we certainly would not exclude that the α-adrenergic blocking effect of ketanserin may contribute as well, as we do not know what

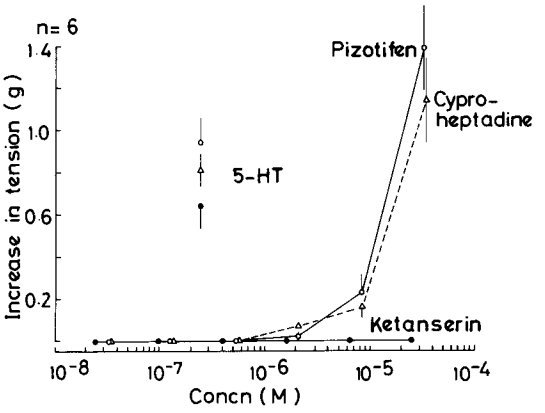


FIG. 1. Demonstration that in the rat jugular vein cyproheptadine (Δ– –Δ) and pizotifen (○—○), but not ketanserin (●—●) cause contractions. Experiments performed on isolated rings studied in isometric conditions, in Krebs-Henseleit solution (for details see Van Nueten et al 1981, 1982). Data shown as means ± s.e.m. (n = 6); for each group of veins the contractile response to $2{\cdot}5 \times 10^{-7}$ M 5-HT is also shown.

* Correspondence.

the exact relationships are between α-adrenergic and 5-hydroxytryptaminergic receptors on vascular smooth muscle cells of the hypertensive blood vessel wall.

REFERENCES


Apperley, E., Feniuk, W., Humphrey, P. P. A., Levy, G. P. (1980) Br. J. Pharmacol. 68: 215–224

Apperley, E., Humphrey, P. P. A., Levy, G. P. (1976) Ibid. 58: 211–221

Cohen, M. L., Fuller, R. W., Wiley, K. S. (1981) J. Pharmacol. Exp. Ther. 218: 421–425

Colpaert, F. C., Niemegeers, J. E., Janssen, P. A. J. (1982) Ibid. 221: 206–214

Fozard, J. R. (1982a) Br. J. Pharmacol. 75 (suppl.): 142P

Fozard, J. R. (1982b) J. Cardiovasc. Pharmacol. 4: 829–838

Humphrey, P. P. A., Feniuk, W., Watts, A. D. (1982) J. Pharm. Pharmacol. 34: 541

Janssen, P. A. J. (1982) in: Yoshida, H., Hagihara, Y., Ebashi, S. (eds) Advances in Pharmacology and Therapeutics II. Pergamon Press, Oxford, pp. 21–33

Kalkman, H. O., Timmermans, P. B. M. W. M., van Zwieten, P. A. (1982) J. Pharmacol. Exp. Ther. 222: 227–231

Leysen, J. E., Niemegeers, C. J. E., Van Nueten, J. M., (1982) Mol. Pharmacol. 21: 301–314

Peroutka, S. J., Snyder, S. H. (1979) Ibid. 16: 687–699

Persson, B., Hedner, T., Henning, M. (1982) J. Pharm. Pharmacol. 34: 442-445

Vanhoutte, P. M. (1978) in: Kaley, G., Altura, B. M. (eds) Microcirculation University Park Press, Baltimore, pp. 181–309

Vanhoutte, P. M. (1982a) in: De Clerck, F., Vanhoutte, P. M. (eds) 5-Hydroxytryptamine in Peripheral Reactions. Raven Press, New York, pp. 163–174

Vanhoutte, P. M. (1982b) TIPS 3: 370–373

Vanhoutte, P. M. (1983) Fed. Proc. Fed. Am. Soc. Exp. Biol. in the press

Vanhoutte, P. M., Van Nueten, J. M., Symoens, J., Janssen, P. A. J. (1982) Ibid. in the press

Van Nueten, J. M., Janssen, P. A. J., De Ridder, W., Vanhoutte, P. M. (1982) Eur. J. Pharmacol. 77: 281–287

Van Nueten, J. M., Janssen, P. A. J., Van Beek, J., Xhonneux, R., Verbeuren, T. J., Vanhoutte, P. M. (1981) J. Pharmacol. Exp. Ther. 218: 217–230

Van Nueten, J. M., Janssen, P. A. J., Vanhoutte, P. M. (1982) in: Bevan, J. A. et al (eds). Vascular Neuroeffectors and Other Smooth Muscles. Raven Press, New York, in the press

Webb, R. C. (1982) Clin Sci. in the press

Wenting, G. J., Man in't Veld, A. J., Woittiez, A. J., Boomsma, F., Schalekamp, M. A. D. H. (1982) Ibid. in the press

Zoccali, C., Zabludowski, J., Isles, C. G., Robertson, J. I. S., Fraser, R., Ball, S. G. (1982) Med. Res. Soc. Edinburgh 9: 19.7


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# The hypotensive action of ketanserin

P. P. A. HUMPHREY*, W. FENIUK, A. D. WATTS, *Department of Pharmacology, Glaxo Group Research Ltd., Ware, Herts, U.K.*

In the reply to our letter Professor Vanhoutte and Dr Van Nueten acknowledge that unequivocal evidence demonstrating a role of 5-hydroxytryptamine in hypertension in man is not available and that the $\alpha_1$-adrenoceptor blocking action of ketanserin may contribute to its hypotensive action. They also quite rightly point out that the relative importance of ketanserin's blocking action on α-adrenoceptors and 5-HT receptors in the hypertensive blood vessel wall remains to be determined (Vanhoutte & Van Nueten 1983). This was precisely the reason for the main suggestion in our original letter (Humphrey et al 1982) that a 5-HT-receptor antagonist without α-adrenoceptor blocking activity should be tested clinically. Parenthetically it does not seem important in this context whether the 5-HT receptor involved is named a "D" or a "5-$HT_2$" receptor, although it is of academic interest. What is important, as we previously pointed out, is that other 5-$HT_2$- or D-receptor blocking drugs are clinically available but they are not used as antihypertensive agents. Whether this is because such drugs also have a concomitant agonistic effect which counterbalances any hypotensive effect is a matter of conjecture. It could equally be postulated that ketanserin, unlike the other 5-HT antagonists, has an additional hypotensive action as yet unidentified which is distinct from its 5-HT-receptor and α-adrenoceptor blocking activity. Since ketanserin is not unique in blocking receptors for 5-HT in the vasculature (Humphrey et al 1982; Cohen et al 1983) it seems *un*reasonable at present to assume that its efficacy *alone* in any given cardiovascular condition is evidence for the pathological involvement of 5-HT, a view shared by others (e.g. see Millar et al 1982; Reimann & Frölich 1983).

* Correspondence

REFERENCES


Cohen, M. L., Mason, M., Wiley, K. S., Fuller, R. W. (1983) Biochem. Pharmacol. 32: 567–570

Humphrey, P. P. A., Feniuk, W., Watts, A. D. (1982) J. Pharm. Pharmacol. 34: 541

Millar, J. A., Facoory, B. D., Laverty, R. (1982) The Lancet Vol 2: 1154

Reimann, I. W., Frölich, J. C. (1983) Lancet 1: 703–704

Vanhoutte, P. M., Van Nueten, J. M. (1983) J. Pharm. Pharmacol. 35: 339–340