Mechanism of action of hydralazine and ISF 2123 on arterial smooth muscle

M. WORCEL

Physiologie et Pharmacologie, INSERM Hôpital Necker, 75015-Paris

The inhibitory action of hydrallazine (HYD) and 3-hydrazino-6-(2-hydroxypropyl)-methylamino piridazine dihydrochloride (ISF 2123) was examined on the rat isolated tail artery perfused at a constant flow. Hydrallazine has been used in the therapy of hypertension for more than 25 years. Despite this long utilization its cellular mechanism of action is still not known (Nickerson, 1970; Van Zweiten, 1968; Köch-Weser, 1976). HYD seems to lower blood pressure through a direct effect on resistance vessels (Stunkard, Wertheimer & Redisch, 1954; Reudi, 1950; Moyer, 1953) and ISF 2123 seems to have the same hemodynamic effects as HYD (Pellegrini & Abbondanti, 1977).

HYD inhibited reversibly the contractions induced by either phenylephrine or serotonin in the distal segments of the caudal artery of normotensive Wistar male rats. Cumulative dose-response curves to HYD were obtained with an ID_{50} of 2.2×10^{-7} M, but the proximal segments were practically unresponsive to HYD. Conversely, both the proximal and distal segments from Okamoto spontaneous hypertensive male rats responded to HYD with an ID_{50} of 1.1×10^{-7} M. After *in vitro* sympathectomy with 6-hydroxydopamine the proximal segments from normotensive rats were inhibited by HYD, and identical responses were then found in proximal and distal segments from normotensive rats, the curve being shifted to the left with an ID_{50} of 1.2×10^{-7} M. No such differences were observed using ISF 2123 which inhibited the proximal and distal segments of artery from the three groups of rats, the ID_{50} being 1.1×10^{-7} M.

It is suggested that HYD and ISF 2123 may interact with a 'receptor' for a biologically occurring molecule. Accordingly the action of non cyclic nucleotides was examined. Adenosintriphosphate (ATP) which is normally released from nerve terminals, did not contract or relax the artery at 10^{-4} M, but it completely blocked the response to HYD of distal segments from normotensive rats, and both proximal and distal segments from hypertensive rats. This effect of ATP is specific, since the response to ISF 2123, which was not affected by the innervation status, was not altered by ATP 10^{-4} M in any of the situations tested. It is concluded that HYD and ISF 2123 act on peripheral arterial smooth muscle, probably on specific receptors which are physiologically affected by ATP or some related substance released from sympathetic nerve terminals. Nonetheless, it seems rather difficult to accept that in this case ATP has a 'transmitter' effect, as it was proposed for some nerve mediated contractile or relaxant effects in smooth muscle by Burnstock, Campbell, Satchell & Smythe (1970), Burnstock, Dumsday & Smythe (1972) and Burnstock (1972).

The technical assistance of F. Da Ponte is gratefully acknowledged.

References

BURNSTOCK, G. (1972). Purinergic nerves. *Pharmac. Rev.*, **24**, 510–581.

BURNSTOCK, G., CAMPBELL, G., SATCHEL, D.G. & SMYTHE, A. (1970). Evidence that adenosine triphosphate or a related nucleotide is the transmitter substance released by non-adrenergic inhibitory nerves in the gut. *Br. J. Pharmac. Chemother.*, **40**, 668–688.

BURNSTOCK, G., DUMSDAY, B., & SMYTHE, A. (1972). Atropine resistant excitation of the urinary bladder: the possibility of transmission via nerves releasing a purine nucleotide. *Br. J. Pharmac. Chemother.*, **44**, 451–461.

KOCH-WESER, J. (1976). Hydralazine. *New Engl. J. Med.*, **295**, 320–323.

MOYER, J.H. (1953). Hydralazine (Apresoline) hydrochloride. *Am. Arch. Int. Med.*, **91**, 415–439.

NICKERSON, M. (1970). Antihypertensive agents and the drug therapy of hypertension. In: *The Pharmacological Basis of Therapeutics*. Goodman and Gilman, 4th Edition Macmillan Co. New York, 728–744.

PELLEGRINI, R. & ABBONDANTI, G. (1977). Characteristics and clinical effects of ISF 2123, a new antihypertensive agent. *Il Farmaco*, **32**, 19–24.

REUBI, F. (1950). Renal hyperemia induced in man by a new phtallazine derivative. *Proc. Soc. exp. Biol., NY*, **73**, 102–103.

STUNKARD, A., WERTHEIMER, L., & REDISCH, W. (1954). Studies on hydralazine, evidence for a peripheral site of action. *J. Clin. Invest.*, **33**, 1047–1053.

VAN ZWEITEN, P.A. (1968). Pharmakologische und biochemische workungen von hydralazin und dihydralazin. *Arzneimittel. Forsch.*, **18**, 79–84.