REVISTA ESPAÑOLA DE FISIOLOGIA, 45 (2), 195-198, 1989

Effects of Selective and Non-Selective β_1-Blockade on Renin Secretion in the Isolated Rat Kidney

J. M. Haro, F. Vargas, M. A. Castillo, L. García-Torres* and D. Acuña**

Departamento de Bioquímica y Biología Molecular
Facultad de Medicina
18012 Granada (Spain)

(Received on May 24, 1988)

J. M. HARO, F. VARGAS, M. A. CASTILLO, L. GARCIA-TORRES and D. ACUÑA. *Effects of Selective and Non-Selective β_1-Blockade on Renin Secretion in the Isolated Rat Kidney.* Rev. esp. Fisiol., 45 (2), 195-198, 1989.

The participation of β_1-adrenoceptor on renin secretion was studied in perfused rat kidney. Administration of propranolol, inhibited the renin release mediated by isoproterenol. Likewise, metoprolol and practolol, showed a similar potency to propranolol in inhibiting isoproterenol-induced renin secretion. These results suggest that the β-receptor responsible for isoproterenol-induced renin release in rats is a β_1-type adrenoceptor.

Key words: Renin secretion, Isoproterenol, Propranolol, Metoprolol, Practolol, β-Adrenoceptor.

Some authors have proposed that β_2-adrenoceptors carry out a major role in controlling renin release. WEBER *et al* (13) have suggested that isoprenaline-induced renin secretion is blocked more effectively by β_2- than β_1-adrenoceptor antagonist. By contrast, other studies (5,7) imply that β_1-adrenoceptors are essential, while β_2-adrenoceptors are considered to be of little importance in causing renin release. On the other hand, it should be noted that most of these studies were carried out in man or in animals *in vivo* (1, 3, 11).

It therefore seems worthwhile to study the role of β_1-adrenoceptor on renin release in an *in vitro* kidney perfusion model. The isolated, perfused rat kidney was chosen because it permits the study of renin secretion under conditions in which extrarenal factors can be controlled.

Materials and Methods

Male Wistar rats weighing 250-300 g were anesthetized with 50 mg/kg sodium pentobarbital i.p. The abdomen was opened by a midline incision and the left kidney, the left renal artery and the abdominal aorta and cava were exposed. Thereafter, the kidney was humidified *in situ* and perfused with warm (37° C) oxygenated Krebs-Ringer dextran saline

* Departamento de Fisiología, Facultad de Medicina, 18012 Granada (Spain).
** To whom all correspondence should be addressed.

(95 % O_2, 5 % CO_2), at a constant rate of 8 ml/min with the help of a Desaga peristaltic pump. The perfusion pressure was continuously monitored by a physiological pressure transducer (type 4-422, Bell and Howel, Ltd.) inserted between the pump and the kidney. Samples were collected after an initial 10 min equilibration period (0 time) and at 5, 10, 15 and 20 min periods thereafter. Isoproterenol and/or β-antagonists were administered through the perfusion fluid with a Braun pump and the animals were grouped as follows: a) Controls: three groups of rats infused with either metoprolol, practolol or propranolol. b) Experimentals: another three groups of rats infused with isoproterenol plus metoprolol, practolol or propranolol. An additional group of rats infused with isoproterenol alone served as controls for this latter group. No changes in perfusion pressure in any of the experimental groups were observed. Perfusate samples were dialyzed successively to pH 4.5 (24 h) and pH 7.5 (24 h) at 4° C with phosphate buffer containing EDTA-Na_2 to remove angiotensinases (12). Samples were then incubated at 37° C for 3 h with nephrectomized rat plasma as substrate (12). The enzymatic reaction was stopped by heating the samples to 85-95° C for 5 min. The angiotensin I was measured by radioimmunoassay. All results are expressed as mean ± SEM. Analysis of signification was performed using the Student's «t» test. The sources and doses of the drugs used were as follows: isoproterenol (Boehringer Ingelheim), 7×10^{-9} M; propranolol (ICI Farma), 3.4×10^{-7} M; practolol (ICI Farma), 1.3×10^{-6} M and metoprolol (Ciba Geigy) 6.3×10^{-6} M.

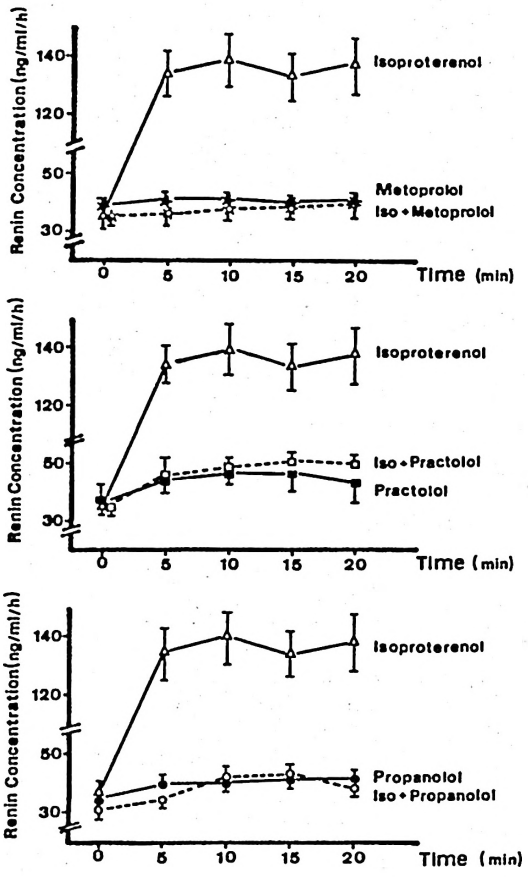

Fig. 1. *Effects of metoprolol (top), practolol (middle) and propranolol (bottom) on renin release induced by isoproterenol.*
Values are given as means ± SEM.

Results

The results (fig. 1) demonstrate that perfusion by any of the β-antagonists, propranolol (n = 6), practolol (n = 6) and metoprolol (n = 6), did not alter basal renin secretion as compared with the control group (n = 6). The β-agonist isoproterenol (n = 5) caused a very significant increase ($p < 0.001$) in renin release compared with the control. The non-selective β-antagonist propranolol (n = 5) blocked the stimulatory effect of isoproterenol on renin secretion (fig. 1, bottom, $p < 0.001$). A similar effect was obtained with selective β_1 blocking agents practolol (n = 5, $p < 0.001$) and metoprolol (n =

5, $p < 0.001$) (fig. 1, middle and top respectively).

Discussion

The β-adrenergic receptor involved in renin response to adrenergic stimulation has been widely investigated. The results, however, are conflicting and vary with the species and the method used. A β-adrenoceptor has been proposed in man (3), cat (7), rabbit (13), dog (5) and rat (2). On the other hand, since factors such as renal hemodynamics and sodium concentration affect renin secretion, the role of the β-adrenoceptor on renin release can be more accurately studied *in vitro*. In fact, the isolated perfused rat kidney permits the investigation of renin under conditions in which these factors can be controlled or excluded.

The results presented here confirm that isoproterenol-mediated renin release occurs in the rat via activation of β_1-adrenoceptors. This is in agreement with previous findings (1, 3, 5) and it suggests that renin release depends upon the β_1-type receptor.

In the present experiments, the effects of two selective β_1-adrenoceptor antagonists, metoprolol and practolol, as well as the nonselective β-antagonist propranolol on renin release induced by isoproterenol (a nonselective β-agonist) *in vitro* were compared. At the dose used, administration of the β-blocker propranolol suppresses the increase in renin secretion caused by isoproterenol, a finding which is in agreement with other studies in rat and man (3).

Of the two selective β_1-antagonists tested, practolol and metoprolol, practolol has been reported to exhibit great selectivity for β_1-blocking effects at a low dose (8), although metoprolol also exerts β_1-blocking properties (11) at a low dosage. In our experiments, practolol and metoprolol are approximately equipotent to propranolol in inhibiting isoproterenol-induced renin secretion.

Some authors, such as WEBER *et al.* (13) have demonstrated that a β_2-blocking agent was responsible for inhibiting isoproterenol-caused renin release. However, isoproterenol can act in two different ways: by affecting the β-adrenoceptor of the juxtaglomerular cells (6) or by affecting the β-adrenoceptor on renal vasculature causing vasodilatation (9). This renal vasodilatation induces renin secretion by activation of the intrarenal vascular presoreceptor, hence, in the study of WEBER *et al.* (13) blockade of these indirect actions of isoproterenol by the β_2-adrenoceptor antagonists could have accounted for their greater effectiveness in blocking renin secretion. It was this finding which led to the suggestion that β_2-adrenoceptor may mediate renin release.

On the other hand, HEALY *et al.* (4) show that β_1-subtype is predominantly contained in juxtaglomerular granule cells and glomeruli, while β_2-subtype is located predominantly in medullary tubules. MILAVEC-KRIZMAN *et al.* (10) showed that β_1-adrenoceptor subtype mediates renin release in the isolated, perfused rat kidney.

To conclude, the present results suggest that renin release induced by isoproterenol from the rat kidney is mediated by a β_1-type adrenoceptor.

Resumen

Se estudia la participación de los receptores β-adrenérgicos en la secreción de renina en el riñón aislado de rata. Los resultados muestran que el propranolol inhibe la liberación de renina mediada por el isoproterenol, mientras que el metoprolol y el practolol muestran una potencia similar al propranolol en la inhibición de la secreción de renina estimulada por el isoproterenol. Estos resultados sugieren que el receptor β-adrenérgico responsable del efecto del isoproterenol sobre la secreción de renina es de tipo β_1.

Palabras clave: Secreción de renina, Isoproterenol, Propranolol, Metoprolol, Practolol, β-Receptor.

References

1. Churchill, P. C., Churchill, M. C. and McDonald, F. D.: *Endocrinology*, 113, 687-692, 1983.
2. Desaulles, E., Miesch, F. and Schwartz, J.: *Br. J. Pharmacol.*, 63, 421-425, 1978.
3. Gavras, I., Gavras, H., Brunner, H. H. and Liang, C. S.: *Br. J. Clin. Pharmacol.*, 2, 213-217, 1979.
4. Healy, D. P., Münzel, P. A. and Insel, P. A.: *Circ. Res.*, 57, 278-284, 1985.
5. Himori, N., Izumi, A. and Ishimori, T.: *Am. J. Physiol.*, 238, F387-F393, 1980.
6. Insel, P. A. and Snavely, M. D.: *Ann. Rev. Physiol.*, 43, 625-636, 1981.
7. Johns, E. I.: *Br. J. Pharmacol.*, 73, 749-754, 1981.
8. Lertora, J. J. L., Mark, A. L., Johannsen, V. J., Wilson, W. R. and Abboud, F. M.: *J. Clin. Invest.*, 56, 719-724, 1975.
9. Lew, R. and Summers, R. J.: *Eur. J. Pharmacol.*, 140, 1-11, 1987.
10. Milavec-Krizman, M., Evenou, J. P., Wagner, H., Berthold, R. and Stoll, A. P.: *Biochem. Pharmacol.*, 34, 3951-3957, 1985.
11. Oates, H. F., Stoker, L. M., Monaghan, J. C. and Stokes, G. S.: *Arch. Int. Pharmacodyn. Ther.*, 234, 205-213, 1978.
12. Skinner, S. L.: *Circ. Res.*, 20, 391-402, 1967.
13. Weber, M. A., Stokes, G. S. and Gain, J. M.: *J. Clin. Invest.*, 54, 1413-1419, 1974.