Direct Relationship Between Urinary Prostaglandin E and Sodium Excretion in Essential Hypertensive Patients

N. PAPANICOLAOU, N. LEFKOS, M. SAFAR, M. PARIS, J. BARIETY and M. MILLIEZ

Centre de Recherches sur l'Hypertension Artérielle, INSERM (U–28), Hôpital Broussais, F–75014 Paris (France); Centre de Recherches sur les Hormones Vasoactives et sur la Physiopathologie Rénale et Vasculaire, Faculté de Médecine de l'Université d'Athènes, Département de Microbiologie, Athènes (Grèce), 24 March 1976.

Summary. Urinary prostaglandins (PGEs and PGFs), sodium and potassium were measured in 17 essentially hypertensive patients. Significant positive correlations were found between a) PGEs secreted in 24 h and sodium excreted in 24 h, b) the ratio PGEs / $U_{Na}V$ before and PGEs / $U_{Na}V$ after volume expansion and c) the ratio Na / K and urinary PGEs. It was suggested that renal PGEs, potent natriuretic and diuretic substances, play an important homeostatic role in the extracellular fluid regulation, and consequently in long-term control of the arterial blood pressure.

The kidney seems to be protected against the vasoconstrictor action of angiotensin II and/or noradrenalin by releasing into the renal venous blood a vasodilator, natriuretic, diuretic and antiadrenergic substance indentified as PGE_2 [1–9]. The release of renal PGE_2 following angiotensin II infusion into the renal artery was confirmed by many investigators who further showed this release and that it was prevented by a potent PGs synthesis inhibitor, indomethacin, and the vasoconstrictor effect of angiotensin II was substantially enhanced [10].

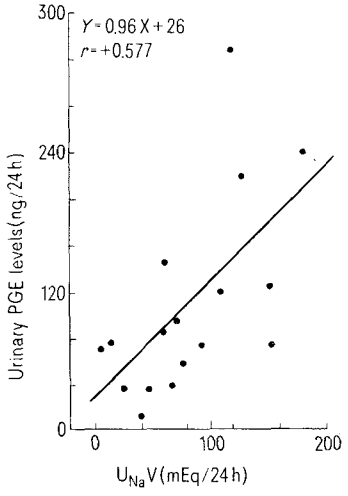

Fig. 1. Significant positive correlation between the PGEs secreted in 24 h and sodium excreted in 24 h in a group of essential hypertensive patients.

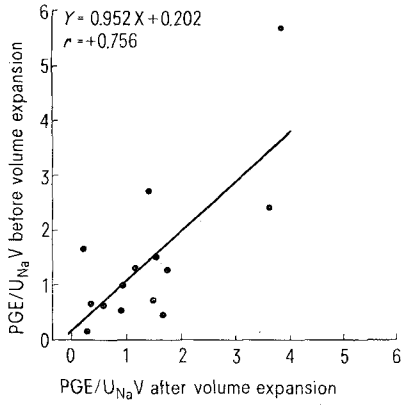

Fig. 2. Significant positive correlation between the ratio of the PGEs secreted in 24 h and sodium excreted in 24 h (PGE/$U_{Na}V$) before and after volume expansion in the same group of patients.

The release of renal PGEs following isotonic saline infusion enforces the hypothesis on the homeostatic role of these substances on the blood volume, blood pressure, sodium and water balance regulation [11–14]. In a previous study we found a significant inverse correlation between the renal PGEs secreted in 24 h and the duration of the hypertensive disease. Significant inverse correlation was also found between the renal PGE_2 secreted in 24 h and the mean blood pressure in the same group of patients [15]. These results enable us to study a) whether a correlation between the renal PGEs secreted in 24 h and sodium excreted in 24 h would also be found in essential hypertensive patients, where a deficiency in renomedullary prostaglandin synthesis and/or release has been suggested to be related to the evolution of the hypertensive disease and b) to evaluate further the possible homeostatic role of the renal PGE_2 and their possible role in the development of the essential hypertension.

Material and methods. The study was performed on 17 hypertensive patients, 11 men and 6 women, of mean age 36 years (23–62 years). All patients underwent a previous complete urography and renal arteriography. The clinical diagnosis was essential hypertention, with a distolic pressure consistently in excees of 100 mm Hg and with no cardiac or neurogenic involvement being noted. These patients were either untreated or had discontinued their therapy at least 1 week before the study. They were kept in the hospital for 6 days and during that time were maintained on a daily sodium and water intake of approximately 100 mEq and 2 liters respectively.

[1] K. SHIMIZU, T. KUROSAWA, T. MAEDA and Y. YOSHITOSHI, Jap. Heart J. *10*, 437 (1969).
[2] H. JOHNSTON, J. HERZOG and D. LAULER, Am. J. Physiol. *213*, 939 (1967).
[3] A. VANDER, Am. J. Physiol. *214*, 218 (1968).
[4] M. FICHMAN, Clin. Res. *18*, 149 (1970).
[5] D. STEINBERG, Ann. N.Y. Acad. Sci. *139*, 897 (1967).
[6] P. HEDQVIST and J. BRUNDIN, Life Sci. *8*, 389 (1969).
[7] U. S. VON EULER and P. HEDQVIST, Acta physiol. scand. *77*, 510 (1969).
[8] N. PAPANICOLAOU, P. MEYER and P. MILLIEZ, J. Pharm. pharmac. *23*, 454 (1971).
[9] J. MCGIFF, K. CROWSHAW, N. TERRAGNO and A. LONIGRO, Nature, Lond. *227*, 1255 (1970).
[10] J. AIKEN and J. VANE, J. Pharmac. exp. Ther. *184*, 678 (1972).
[11] N. PAPANICOLAOU, Experientia *28*, 275 (1972).
[12] N. PAPANICOLAOU, J. Pharm. Pharmac. *27*, 704 (1975).
[13] K. SHIMIZU, M. YAMAMOTO and Y. YOSHITOSHI, Jap. Heart J. *14*, 140 (1973).
[14] N. PAPANICOLAOU, TH. MOUNTOKALAKIS, M. SAFAR, G. SOTIROPOULOU, J. BARIETY and P. MILLIEZ, Int. Conf. on Prostaglandins, Florence, May 26–30 1973, p. 138.
[15] N. PAPANICOLAOU, TH. MOUNTOKALAKIS, M. SAFAR, J. BARIETY and P. MILLIEZ, Experientia *32*, 1015 (1976).

Mean values and SEM, of the age in years, the mean blood pressure (MBP mm Hg), urinary prostaglandins E and F secreted per 24 h (PGEs ng/24 h and PGFs ng/24 h), sodium and potassium rejected per 24 h ($U_{Na}V$ mEq/24 h and U_KV mEq/24 h) and the ratio between Na/K, before (B. Ex.) and after (A. Ex.) extracellular space expansion by 2 l of isotonic saline, infused at the rate of 0.3 ml/kg/min in the group of the essential hypertensive patients

	n	Age (years)	MBP (mm Hg)	PGEs (ng/24 h)	PGFs (ng/24 h)	$U_{Na}V$ (mEq/24 h)	U_KV (mEq/24 h)	V (ml/24 h)	Na/K
B. Ex.	17	36 (23–62)	126±5	105±27	66±27	83±13	54±4	1483±390	2.04±0.33
A. Ex.	14	37 (23–62)	116±6	327±63	123±48	237±17	67±5	2592±677	3.73±0.44
	$p <$	NS	0.1	0.003	NS	0.001	0.025	0.001	0.005

The following parameters were measured before and after extracellular space expansion[16,17]. 1. Arterial blood pressure was measured 4 times a day. Mean blood pressures (MBP) were calculated from the diastolic (DBP) and systolic (SBP) pressures by the formula MBP = (2DBP + SBP): 3. The mean value of the 4 mean blood pressures was taken.

2. Prostaglandins. Bioassays were performed on extracts of 500 ml, from 24 h urine collections, after chromatographic separation into PGE and PGF groups[18,19]. The method used was described in details elsewhere[15]. Since PG metabolites appearing in the urine generally have less biological activity than the parent compound[20]. It might be assumed that most of the biologically active substances detected in this study were natural PGs.

3. Urinary output of sodium ($U_{Na}V$) and potassium (U_KV) are calculated by the usual methods. Electrolyte concentration was measured by flame photometer (Eppendorf).

Results and discussion. The results are summarized in the Table. A significant positive correlation was found between the PGEs secreted in 24 h and sodium excreted ($U_{Na}V$) in 24 h (Figure 1). After isotonic saline infusion, sodium excreted in 24 h was directly proportional to the increase in PGEs release following saline infusion (Figure 2). We did not find any correlation between the PGFs and sodium excreted either before or after saline infusion. The release of prostaglandins following either intravascular and/or extracellular space expansion is well known[11–14], and is confirmed by this study.

These results suggest that the major role of PGEs could consist in the regulation of the extracellular fluid, and consequently in the longterm control of arterial blood pressure, and that the deficiency in renomedullary PG synthesis, related to the evolution of essential hypertension[15], could be the cause and/or the result of the hypertensive disease. Finally the positive significant correlation found between the ratio of urinary Na/K and urinary PGEs ($Y = 0.015X + 0.53$, $r = 0.672$), could suggest an antagonistic result between these substances (PGEs) and the aldosterone system.

[16] Of these 17 patients 3 of them, did not undergo expansion.

[17] Extracellular space was expanded by i.v. infusion of 2 l of isotonic saline at the rate of 0.3 ml/kg/min.

[18] PGE and PGF group was assayed as ng of PGE_2 and $PGF_{2\alpha}$ equivalent respectively. Standard PGE_2 and $PGF_{2\alpha}$ were kindly provided by Dr J. Pike, Upjohn Company Kalamazoo Mich.

[19] In view of the continuing controversy on the self existence of PGAs. M. Hamberg, FEBS Lett. 5, 127 (1969). – J. Hinman, A. Rev. Biochem. *41*, 161 (1972). – J. McGiff, K. Crowshaw and H. Itskovitz, Fedn. Proc. *33*, 39 (1974); only PGE and PGF groups were assayed in this study.

[20] P. Piper, in *Prostaglandins. Pharmacological and Therapeutic Advances* (Ed. M. Guthbert; Heineman, London 1973), p. 126.

The Action of Cycloheximide on the Action Potential and Protein Synthesis in Medullated *Xenopus* Axons

G. Al-Zahid, G. M. Schoepfle and W. F. Bridgers

Department of Physiology and Biophysics, Neurosciences Program, University of Alabama in Birmingham, University Station, Birmingham (Alabama 35294, USA), 8 March 1976.

Summary. Cycloheximide depresses maximum rate of change in membrane potential observed during the rising phase of the action potential in single medullated axons of *Xenopus*. Time course of depression is independent of cycloheximide concentration over a range that almost completely inhibits leucine incorporation into axonal proteins.

Under conditions of continuous fluid exchange, cycloheximide, a potent inhibitor of ribosomal protein synthesis, induces a gradual depression in the maximum rate of change in membrane potential observed during the rising phase of the action potential in an isolated medullated nerve fibre of *Xenopus*. Experimental results are illustrated in Figures 1 and 2.

The progressive increase in $\dot{V}$ associated with the 10 mg/l concentration of cycloheximide is quite often observed in control experiments, most of which, however, involve an unexplained rise in $\dot{V}$ to a plateau level throughout a time course of several hours.

However, depressive effects when present, can be reversed by means of a brief conditioning hyperpolarization under conditions such that the maximal value attained by $\dot{V}$ is identical with that which would have been obtained from a normal or non-depressed fibre after conditioning hyperpolarization. Supporting data were obtained from monitoring experiments similar to those involving recent investigations of taxine action[1].

[1] J. R. Smythies, F. Benington R. D. Morin, G. Al-Zahid and G. M. Schoepfle, Experientia *31*, 337 (1975).