REVISTA ESPAÑOLA DE FISIOLOGIA, 42 (2), 257-264. 1986

Dopamine Control of Aldosterone Secretion in End-Stage Renal Failure

R. García-Robles, L. Ruilope *, J. Tovar, L. F. de Villa *, B. Miranda *, C. Prieto *, J. Parada, J. Sancho and J. L. Rodicio *

Servicio de Endocrinología
Centro Ramón y Cajal
28034 Madrid (Spain)

(Received on September 3, 1985)

R. GARCIA-ROBLES, L. RUILOPE, J. TOVAR, L. F. DE VILLA, B. MIRANDA, C. PRIETO, J. PARADA, J. SANCHO and J. L. RODICIO. *Dopamine Control of Aldosterone Secretion in End-Stage Renal Failure*. Rev. esp. Fisiol., 42 (2), 257-264. 1986.

The role of the tonic inhibitory effect of dopamine on aldosterone secretion has been investigated in 10 patients with chronic renal failure (CRF) on hemodialysis, in 8 normotensive renal transplant recipients (Tx) with normal renal function and in 8 normotensive volunteers (NV). The following tests were performed: 1) the response of plasma aldosterone (PA) to metoclopramide administration; 2) the response of plasma prolactin (PRL) to TRH administration, and 3) the changes induced by Lisuride (a dopaminergic agonist, on the values of PA and PRL). The basal values of PA and PRL were higher in CRF than in NV and Tx. The inverse was true for plasma renin activity (PRA) values. The response of PA and PRL to metoclopramide showed blunted increases in CRF when compared to NV, in the absence of changes of PRA, cortisol and potassium. After TRH administration, PRL increase in CRF was also inferior. Lisuride induced a decrease of both PA and PRL both in CRF and NV. In Tx, basal values of PA and PRL were similar to NV. Nevertheless, the response to metoclopramide and TRH were partially blunted when compared to that of NV. These results point to the existence of a deranged dopaminergic regulation of aldosterone secretion in end-stage renal failure patients. The alterations are partially corrected by a well-functioning kidney graft.

Key words: Aldosterose, Dopamine, Dopamine agonist, Renal failure, Renal transplant.

The existence of an increased aldosterone secretion rate in chronic renal failure was described more than two decades ago by COPE and PEARSON (7). More recently these results have been confirmed through the measurement of plasma aldosterone levels (16, 26). The renin-angiotensin system and plasma potassium levels have been recognized as the two major determinants of aldosterone secretion in this particular condition (2, 26), and the participation of ACTH does not seem to be as important as in other situations (27).

The original description of NORBIATO *et al.* (21) on the effect metoclopramide

* Servicio de Nefrología. Ciudad Sanitaria «1.º de Octubre», Madrid (Spain).

administration on plasma aldosterone has led to the consideration of dopamine as a new factor in the regulation of aldosterone secretion. Dopamine seems to exert a tonic inhibitory effect on the rate of aldosterone secretion by the adrenal gland (3, 4). In chronic renal failure the existence of a derangement of the dopaminergic control of other hormonal systems such as the control of prolactin has been sought (11). These facts prompted us to investigate the state of the dopaminergic regulation of aldosterone secretion in chronic renal failure as compared with that of normal volunteers and a group of renal transplant patients with a well-functioning graft. The objective was achieved through the study of the response of plasma aldosterone to metoclopramide administration, the response of plasma prolactin to TRH administration and through the investigation of the effect of Lisuride (a dopaminergic agonist) on the above mentioned hormones.

Materials and Methods

Patients. A group of 10 normotensive patients (6 male, 4 female, 22-56 years old, means = 38.5) diagnosed as having chronic renal failure (CRF) and undergoing hemodialysis treatment for at least 6 months were included in the study. All of them were maintained on a diet containing 1 g of protein per kg of body weight with a sodium intake of about 100 mEq daily. They were dialysed tree times a week for four hours with a capillary dialyzer. All of them were taking aluminum hydroxyde plus vitamins as their only medication. A second group of 8 transplant patients (Tx) (6 males, 2 females, 26 to 51 years old, means = 37.6) who received a cadaver kidney transplant at least 6 months prior to the performance of the tests was also studied. All of them were normotensive and had a maintained serum creatinine below 1.5 mg/dl. They received as the only medications prednisone 10 mg every other day and azathioprine 1-1.5 mg/kg of body weight/daily. Sodium and protein intake were not restricted. A further group of eight normotensive age-matched (26-49 years old) male volunteers (NV) with normal renal function was also investigated. They were on an ad libitum sodium diet. No alcohol intake or smoking were allowed in three groups on the day the tests were performed. Patients and volunteers were hospitalized during the studies. A signed consent was obtained from every patient and volunteer and the protocol was accepted by the Ethics Committee of the Hospital.

Experimental procedures. Patients and volunteers were admitted to the Hospital and the following tests were performed in the fasting state and after overnight recumbency:

1) The basal values and the response of plasma aldosterone (PA), renin activity (PRA), cortisol, prolactin (PRL) and potassium to the administration of metoclopramide (an i.v. bolus of 10 mg). Blood samples were drawn at time 0 before metoclopramide administration and 10, 15, 20 and 60 minutes afterwards.

2) The basal values and the response of plasma PRL to the administration of TRH (an i.v. bolus of 200 μg). Blood samples were drawn at time 0 before TRH administration and 15, 30 and 60 minutes later.

3) In volunteers and CRF patients the effect of the administration of a dopaminergic agonist (Lisuride 0.025 mg t.i.d. orally during two weeks) on the values of PRL, PA, PRA and K have also been investigated.

4) In CRF values of PA, PRL, potassium and cortisol were repeated after 1 hour of isolated ultrafiltration and

also after 4 hours of a standard dialysis without weight loss.

Every blood sample was immediately centrifuged at 4°C and plasma samples were frozen at —20°C until assayed. Experiments 1 and 2 were performed in the absence of postural changes. In CRF patients, tests 1 and 2 were performed the day after hemodialysis. In renal patients the tests were performed the day without prednisone intake.

Analytical methods. The measurement of PRA was performed by the method of HABER *et al.* (14) with the modifications published elsewhere (8). The PA levels were determined according to SANCHO and HABER (23), plasma PRL and cortisol by specific radioimmunoassay (9, 25) and the potassium levels by standard laboratory techniques.

Statistical methods. All values are expressed by a mean standard deviation. Differences in the values determined before and after TRH and metoclopramide administration were obtained for each group by the Wilcoxon test for paired data. The variations between the three groups in the secretion rate of PA and PRL in response to TRH and metoclopramide were analysed by the Kruskell-Wallis (ANOVA) test, followed by the Mann-Withney test for impaired data. For this comparison the levels obtained at time 0 and the maximal increase after metoclopramide or TRH administration were used.

Results

The study of the basal values of PA and PRL showed, as contained in table I, higher values in CRF patients than in NV and Tx This finding was accompanied by lower levels of PRA and by increased levels of potassium in the absence of changes in serum cortisol. Isolated ultrafiltration induced in CRF patients a significant increase of both PRA and PA without changes of potassium. The dialysis did not change these values but decreased significantly those of serum potassium.

The administration of metoclopramide induced significant increases of both PA and PRL in the three groups studied. Nevertheless the increase of PA and PRA was significantly lower in the CRF patients when compared with NV but not when compared with Tx. No significant changes were observed for PRA, cortisol or potassium in any of the groups studied (table II).

The response of plasma PRL to the administration of TRH shows an increase of PRL in every group studied, but this

Table I. *Basal values of plasma aldosterone (PA), renin activity (PRA), prolactin (PRL), potassium (K) and cortisol (F) in CRF patients, NV and Tx.*
Values expressed as means ± S.D. [a] CRF before dialysis patients; [b] CRF after isolation ultrafiltration; [c] CRF after dialysis.

Group	(n)	PA ng/dl	PRA ng/ml/h	PRL ng/ml	K mEq/l	F µg/dl
CRF[a]	10	5.9 ± 2.0	1.9 ± 1.3	71.0 ± 59.8	5.0 ± 0.2	12.0 ± 2.5
CRF[b]		11.1 ± 1.3**	3.6 ± 1.2**	76.3 ± 52.1	5.1 ± 0.3	11.8 ± 3.0
CRF[c]		10.9 ± 1.2**	4.2 ± 1.2**	83.2 ± 47.9	3.1 ± 0.2**	11.9 ± 2.3
NV	8	4.1 ± 0.6*	3.1 ± 0.5***	11.0 ± 0.9**	4.5 ± 0.3**	12.2 ± 1.4
Tx	8	4.2 ± 1.3*	3.2 ± 0.3**	4.1 ± 0.9**	4.3 ± 0.5**	12.2 ± 6.7

* $p < 0.05$ *vs* before dialysis; ** $p < 0.01$ *vs* CRF before dialysis; *** $p < 0.025$ vs CRF before dialysis.

Table II. *Values of plasma prolactin (PRL), aldosterone (PA), renin activity (PRA), cortisol (F), and potassium (K), before (point 0) and after administration of metoclopramide in normotensive volunteers (NV), chronic renal failure (CRF) and renal transplant patients (Tx).* Values expressed as means ± S.D.

	Time (min)				
	0	10	15	20	60
NV (8)					
PRL (ng/ml)	11.0 ± 0.9	84.1 ± 30.6*	108.1 ± 21.6*	98.9 ± 15.2*	70.2 ± 30.5**
PA (ng/dl)	4.1 ± 0.6	12.1 ± 3.9**	15.3 ± 5.0**	12.2 ± 4.0**	7.6 ± 2.5
PRA (ng/ml/h)	3.1 ± 0.5	3.3 ± 0.5	3.2 ± 0.7	2.6 ± 0.4	3.4 ± 0.3
F (μg/dl)	12.2 ± 1.4	13.5 ± 1.5**	12.6 ± 0.6	13.2 ± 0.8	12.3 ± 0.7
K (mEq/l)	4.5 ± 0.3	4.4 ± 0.3	4.5 ± 0.1	4.5 ± 0.1	4.5 ± 0.1
CRF (10)					
PRL (ng/ml)	71.0 ± 59.8	110.1 ± 75.2*	116.5 ± 74.7*	118.8 ± 78.9*	107.9 ± 74.9*
PA (ng/dl)	5.9 ± 2.0	10.1 ± 4.5*	9.8 ± 3.5*	9.2 ± 3.5*	8.9 ± 4.1*
PRA (ng/ml/h)	1.9 ± 1.3	2.2 ± 1.4	2.3 ± 1.3	2.1 ± 1.1	2.0 ± 1.0
F (μg/dl)	12.0 ± 2.5	11.5 ± 3.3	11.7 ± 2.1	12.2 ± 2.0	13.0 ± 1.7
K (mEq/l)	5.0 ± 0.2	5.0 ± 0.3	4.9 ± 0.2	5.0 ± 0.3	5.0 ± 0.3
Tx (8)					
PRL (ng/ml)	4.1 ± 0.9	67.0 ± 54.8*	90.5 ± 55.6*	104.5 ± 55.0*	94.5 ± 56.9*
PA (ng/dl)	4.2 ± 1.3	11.9 ± 3.8*	12.0 ± 3.9*	12.0 ± 7.7*	8.2 ± 5.3***
PRA (ng/ml/h)	3.2 ± 0.3	3.1 ± 1.8	3.0 ± 1.7	2.9 ± 2.0	3.1 ± 1.6
F (μg/dl)	12.0 ± 2.5	12.6 ± 6.7	12.1 ± 6.5	12.4 ± 6.1	10.9 ± 5.7***
K (mEq/l)	4.3 ± 0.5	4.4 ± 0.4	4.3 ± 0.3	4.3 ± 0.2	4.3 ± 0.1

p *vs* time 0: * < 0.001; ** < 0.02; *** < 0.05.

Table III. *Response of plasma prolactin (PRL) to the administration of TRH in normotensive volunteers (NV), chronic renal failure patients (CRF) and renal transplantation (Tx).* Values expressed as means ± S.D.

		Time (min)			
Group	n	0	15	30	60
NV	8	10.2 ± 1.8	59.9 ± 11.7*	36.4 ± 6.8*	19.3 ± 2.1*
CRF	10	60.2 ± 16.3	68.6 ± 53.3*	71.2 ± 52.2**	69.7 ± 23.2***
Tx	8	3.6 ± 0.7	20.8 ± 15.6*	14.1 ± 9.2*	7.1 ± 3.1

p *vs* time 0: * < 0.01; ** < 0.02; *** < 0.05.

Table IV. *Values of PA, PRA, PRL and potassium (means ± S.D.), before and after Lisuride administration in CRF and NV.*

	CRF (n = 10)			NV (n = 8)		
	Before	After	P	Before	After	P
PA (ng/dl)	5.9 ± 2.0	1.7 ± 1.8	< 0.001	4.7 ± 2.7*	4.1 ± 2.5*	< 0.05
PRA (ng/ml/h)	1.9 ± 1.3	2.0 ± 1.6	NS	5.6 ± 4.0*	4.6 ± 1.7*	NS
PRL (ng/ml)	71.0 ± 59.8	23.3 ± 22.0	< 0.01	10.2 ± 1.8	4.5 ± 0.9	< 0.01
K^+ (mEq/l)	5.1 ± 0.3	5.2 ± 0.2	NS	4.4 ± 0.2	4.3 ± 0.3	NS

* Values obtained after 3 hours of ambulation. NS = no significant.

was significantly higher in NV than in CRF and Tx patients (table III).

The administration of Lisuride induced a significant decrease of PA in CRF patients and NV without concomitant changes of PRA or K. The same was true for PRL levels.

Discussion

Classically the factors known to be involved in the control of aldosterone secretion by the adrenal gland are angiotensin II, ACTH and potassium. COPE and PEARSON (7) described the existence of an increased secretion rate of aldosterone in chronic renal failure. In accordance with this, augmented plasma levels of aldosterone have been found in patients with creatinine clearance values below 50 % of normal (16). Our finding of elevated basal values of aldosterone levels in patients with terminal renal failure on hemodialysis are in agreement with previous descriptions. In addition our finding is accompanied by lower levels of plasma renin activity and higher values of potassium and by similar levels of plasma cortisol. A possible interpretation of these results would be that in our patients plasma aldosterone is inadequately elevated when compared with plasma renin activity. This fact, does not seem to be due to changes in ACTH according to the similar levels of plasma cortisol, but could well be the consequence of the elevated serum potassium levels. Nevertheless, the absence of a decrease in plasma aldosterone when the serum potassium fell as a consequence of dialysis points to the existence of other factors as the cause of the increased plasma aldosterone levels. As described in other situations such as in the so-called low renin essential hypertension (28) an increased adrenal sensitivity to angiotensin II, could be invoked to explain our findings Since the original description of CAREY *et al.* (3, 4) it has been admitted that dopamine exerts a tonic inhibitory effect on aldosterone secretion which is independent of the state of sodium balance of the subject (10, 12). The appearance of an increased secretion rate of aldosterone by the adrenal in patients with chronic renal failure could then be the consequence of a deranged dopaminergic control of aldosterone secretion. When metoclopramide was administered to our patients with chronic renal failure the response of plasma aldosterone was significantly lower than in normotensive volunteers. A blunted response of plasma aldosterone to the administration of a dopamine antagonist, could be expected whenever a diminished function of dopamine

existed. The diminution of the levels of plasma aldosterone when Lisuride, a dopamine agonist (13) was administered also favours our hypothesis.

There is considerable evidence that dopamine plays a major role in the regulation of prolactin release (6). Furthermore dopamine is a PRL inhibitory factor (5, 18). Chronic renal failure is frequently accompanied by the existence of hyperprolactinemia (11) that usually responds favourably to the administration of dopamine agonist drugs (19, 20). Our findings are in agreement with these reports. The increase of the prolactin levels in the plasma of patients with chronic renal failure has been attributed to a diminished renal metabolism of the hormone (22). Nevertheless the existence of an elevated secretion rate of prolactin has been shown in chronic renal failure (11). This fact has been interpreted as due to the existence of an insensitivity of the lactotrophs to stimulation (24) similar to that described in pathological hyperprolactinemia of other origin (1). The present data confirm the existence of hyperprolactinemia in chronic renal failure that responds to the administration of a dopamine agonist and that shows a blunted response to both TRH and metoclopramide. This finding could depend on the existence of a deranged dopaminergic system (15). Furthermore the positive response to the administration of a dopamine agonist in the presence of lactotroph resistance also favours the hypothesis of the existence of a diminished dopamine regulation of prolactin in chronic renal failure. Recently in another situation of hyperprolactinemia, the resistance of the lactotrophs to dopamine has been discarded as the cause of the elevation of prolactin (17).

Finally, our findings support the statement that the increased plasma levels of aldosterone found in patients with chronic renal failure could be due to the existence of a deranged dopaminergic control of aldosterone secretion The role of potassium is, ruled out, because when the dopamine agonist is administered, plasma aldosterone falls in the absence of changes in plasma potassium levels. The derangement of dopaminergic system also contributes to the appearance of hyperprolactinemia, which shows blunted responses to metoclopramide and TRH, which responds to the administration of a dopamine agonist.

Renal transplantation has been recognized as able to reverse many of the clinical manifestations of uremia. The alteration of prolactin seen in chronic renal failure reverses with a successful renal transplant (22). These findings in respect to basal values are in accordance. Nevertheless, the response of aldosterone and prolactin to metoclopramide and of PRL to TRH administration is not different from that of CRF patients. It suggests that alteration of aldosterone and prolactin secretion rate is only partially corrected after the performance of a successful kidney transplant. We cannot exclude that long-term steroid treatment participates in these events.

Acknowledgements

We are gratefully indebted to Schering AG Berlin for the supply of Lisuride tablets. We also acknowledge Miss E. Ramos and M. C. Casal for their technical assistance and Miss C. Sarabia for manuscript typewriting.

Resumen

Se estudia el efecto inhibitorio del sistema dopaminérgico sobre la secreción de aldosterona y PRL en pacientes con insuficiencia renal crónica en estadio terminal y en pacientes portadores de trasplante renal, mediante la administración de metoclopramida y TRH, en situación basal y tras la toma de un agonista dopaminérgico (Lisuride), comparándose los resultados obtenidos con los de un grupo de voluntarios sanos. Los valores basales de al-

dosterona plasmática y PRL son más altos en los pacientes con insuficiencia renal crónica que en los trasplantados y en los voluntarios sanos. Por el contrario, la respuesta de ambas hormonas a la metoclopramida es menor. La adición del agonista dopaminérgico induce disminución de los valores basales de aldosterona y PRL en el grupo de insuficiencia renal crónica. Los datos obtenidos parecen indicar una disfunción del control dopaminérgico sobre aldosterona, en pacientes con insuficiencia renal en estadios terminales.

References

1. Bansal, S., Lee, L. A. and Woolf, P. D.: *Am. J. Med.*, **71**, 961-972, 1981.
2. Bayard, F., Cooke, R. C., Tiller, D. J., Beitins, I. S., Kowarski, A., Walker, W. G. and Migeon, C. J.: *J. Clin. Invest.*, **50**, 1585-1595, 1971.
3. Carey, R. M., Thorner, M. O. and Ortt, E. M.: *J. Clin. Invest.*, **63**, 727-735, 1979.
4. Carey, R. M., Thorner, M. O. and Ortt, E. M.: *J. Clin. Invest.*, **66**, 10-18, 1980.
5. Caron, M. G., Beaulieu, M., Raymond, V., Gagne, B., Drouin, J., Lefkowitz, J. and Labrie, F.: *J. Biol. Chem.*, **253**, 2244-2253, 1978.
6. Clemens, J. A., Shaar, C. J. and Smalsay, E. B.: *Fed. Proc.*, **39**, 2907-2912, 1980.
7. Cope, C. L. and Pearson, J.: *Clin. Sci.*, **25**, 331-341, 1963.
8. Epstein, M., Levinson, R., Sancho, J., Haber, E. and Re, R.: *Cir. Res.*, **41**, 818-829, 1977.
9. Foster, L. B. and Dunn, R. T.: *Clin. Chem.*, **20**, 365-368, 1974.
10. García-Robles, R., Ruilope, L., Mancheño, E., Hurtado, A., Alcázar, J. M., Varela, C., Calle, H., Rodicio, J. L. and Sancho, J.: *Rev. esp. Fisiol.*, **40**, 63-68, 1984.
11. Giedersten, G. D., Lim, V. S., Nakawatase, C. and Frohman, L. A.: *J. Clin. Endocrinol. Metab.*, **50**, 846-852, 1980.
12. Gordon, M. B., Moore, T. J., Dluhy, R. G. and Williams, G. H.: *J. Clin. Endocrinol. Metab.*, **56**, 340-345, 1983.
13. Graf, K. I., Schmidt-Gollwitzer, M., Horowski, R. and Dorow, R.: *Clin. Endocrinol.*, **17**, 243-251, 1982.
14. Haber, E., Koerner, T., Page, L. B., Kliman, B. and Purnode, A.: *J. Clin. Endocrinol. Metab.*, **29**, 1349-1354, 1969.
15. Healy, D. L. and Burger, H. G.: *J. Clin. Endocrinol. Metab.*, **46**, 709-714, 1978.
16. Hene, R. J., Boer, P., Koomans, H. A. and Dorhout Mees, E. J.: *Kidney Int.*, **21**, 98-101, 1982.
17. Ho, K. Y., Smythe, G. A., Duncan, M. and Lazarus, L.: *J. Clin. Endocrinol. Metab.*, **58**, 128-133, 1984.
18. Mac Leod, R. M. and Lehmeyer, J. F.: *Endocrinology*, **94**, 1077-1085, 1974.
19. Martínez-García, J. M., García-Robles, R., Ruilope, L., Morales, J. M., Nieto, J., Alcázar, J. M., Barrientos, A., Rodicio, J. L. and Sancho, J.: *Nefrología*, **2**, supl. 1, 52, 1983.
20. Muir, J. W., Besser, G. M., Edwards, C. R. W., Rees, L. H., Cattell, W. R., Ackrill, P. and Baker, L. R. I.: *Clin. Nephrol.*, **20**, 308-314, 1983.
21. Norbiato, G., Bevilacqua, M., Raggi, U., Micossi, P. and Moroni, C.: *J. Clin. Endocrinol. Metab.*, **45**, 1313-1316, 1977.
22. Pecos, R., Horcajada, C., López-Novoa, J. M., Frutos, M. A., Casado, S. and Hernando, L.: *Nephron*, **28**, 11-16, 1981.
23. Sancho, J. and Haber, E.: *J. Clin. Endocrinol. Metab.*, **47**, 391-396, 1978.
24. Schwitz, O. and Holler, J.: *Acta Endocrinol.*, **102**, 486-491, 1983.
25. Sinha, Y. N., Selby, F. W., Lewis, V. J. and Vanderlaan, W. P.: *J. Clin. Endocrinol. Metab.*, **36**, 509-516, 1979.
26. Weidmann, P., Maxwell, M. H. and Lupu, A. N.: *Ann. Intern. Med.*, **78**, 13-18, 1973.
27. Williams, G. H., Bailey, G. L., Hampers, C. L., Lauler, D. P., Merrill, J. P., Underwood, R. H., Blair-West, J. R., Coghlan, J. P., Denton, D. A., Scoggins, B. A. and Wright, R. D.: *Kidney Int.*, **4**, 280-288, 1973.
28. Wisgerhof, M. and Brown, R. D.: *J. Clin. Invest.*, **61**, 1456-1462, 1978.