REVISTA ESPAÑOLA DE FISIOLOGIA. 40, 63-68 1984

Dopaminergic Modulation of Aldosterone Secretion: Effect of Sodium Balance and Postural Changes

R. García-Robles, L. Ruilope*, E. Mancheño, A. Hurtado, J. M. Alcázar*, C. Varela, H. de la Calle, J. L. Rodicio* and J. Sancho

Servicio de Endocrinología
Centro «Ramón y Cajal»
Madrid (Spain)

(Received on June 29, 1983)

R. GARCIA-ROBLES, L. RUILOPE, E. MANCHEÑO, A. HURTADO, J. M. ALCAZAR, C. VARELA, H. DE LA CALLE, J. L. RODICIO and J. SANCHO. *Dopaminergic Modulation of Aldosterone Secretion: Effect of Sodium Balance and Postural Changes.* Rev. esp. Fisiol., 40, 63-68. 1984.

The influence of an increased endogenous production of angiotensin II and of sodium homeostasis upon the response of plasma aldosterone to metoclopramide administration has been investigated in 5 normal volunteers. Our results show that the increase of plasma aldosterone after metoclopramide administration is independent of angiotensin II, ACTH and potassium, and that it increases even further due to the endogenous production of angiotensin II induced by postural changes. The state of sodium balance seems to influence the response of plasma aldosterone to metoclopramide administration as it occurs with other stimuli of aldosterone secretion.

Key words: Angiotensin II, Aldosterone, Metoclopramide, ACTH, Sodium homeostasis, Postural changes.

Recent data suggest that aldosterone secretion is under tonic dopaminergic inhibition in normal man (3, 4, 7). The role of dopamine in the aldosterone control rests largely on the aldosterone response to metoclopramide administration (3, 4, 7). CAREY *et al.* (3) have postulated that the dopaminergic control of aldosterone secretion is maximum and can be overridde by the administration of exogenous angiotensin II in normal man. Very recently (17) it has been postulated that sodium homeostasis may influence the dopaminergic modulation of aldosterone secretion.

The aim of this study was double; investigate whether or not the increased secretion of aldosterone induced by metoclopramide administration was overridden by an increased endogenous production of angiotensin obtained through postural changes and second whether

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

or not this response is influenced by the sodium balance of the subject.

Materials and Methods

Five male volunteers normotensive between 21 and 25 years old, were included in the study. Metoclopramide (10 mg i.v.) and placebo were administered in two situations of sodium balance: while taking *ad libitum* sodium diet, and after 7 days on a diet containing 20 mEq of sodium and 40 mEq of potassium daily. After overnight recumbency plasma samples were obtained at intervals of —30, —15, 0, 10, 15, 20, 30, 60, 90 and 120 minutes. The subjects remained in the supine position until the blood sample of 60 min was obtained and deambulation was initiated thereafter.

In every plasma sample, plasma renin activity (PRA), aldosterone, prolactin (PRL), cortisol and potassium were measured. The adequacy of the low sodium intake was established through the measurement of 24-hour urinary sodium and potassium excretion that had to be less than 30 mEq and 50 mEq respectively on the sixth day of the diet.

Sodium and potassium were measured by standard laboratory techniques. Plasma renin activity was measured by radioimmunoassay according to the method of HABER *et al.* (11) modified as described elsewhere (8). Plasma aldosterone was measured following the method of SANCHO and HABER (15) and PRL and cortisol were determined by specific radioimmunoassay according to the methods of SINHA *et al.* (16) and FOSTER and DUNN (9) respectively.

Statistical analysis was carried out with the double tailed t test for paired data.

Results

Table I contains the values of PRA, plasma aldosterone, PRL, plasma cortisol and potassium obtained while on a sodium *ad libitum* diet with the administration of placebo and metoclopramide. Table II contains the values of the same parameters after 7 days on a low sodium diet with the administration of placebo and metoclopramide.

The values of PRA and plasma aldosterone were, as expected, higher in the sodium depleted state ($p < 0.01$) and its behaviour was similar independent of the sodium balance of the subject. Plasma aldosterone increased significantly ($p < 0.01$) after metoclopramide administration with peak values at 15 minutes, although the maximum percent change variation was higher after metoclopramide while on a low sodium diet (194 vs 163). Deambulation induced further increases in plasma aldosterone levels although the percent change was lower after metoclopramide administration in both situations of sodium balance (at 120 min 122 vs 269 in *ad libitum* sodium diet and 118 vs 301 after sodium restriction).

The levels of PRA were not modified after the administration of placebo nor metoclopramide and showed similar increments with deambulation in any of the situations studied. Plasma PRL increased significantly ($p < 0.01$) with metoclopramide in both situations of sodium balance reaching its highest peak between 20 and 30 minutes after the administration of te drug. The maximun percent variation was also higher while on a low sodium diet (160 vs 130).

Discussion

Since the original description of NORBIATO *et al.* (14) it has been accepted that the administration of metoclopramide, a competitive antagonist of dopamine, increases the aldosterone secretion in the normal subject. The present results confirm this finding and exclude the role of

Table I. *Values of PRA, plasma aldosterone (PA), PRL, cortisol (F) and potassium (K) while taking and* ad libitum *sodium diet obtained with the administration of placebo (P) or metoclopramide (M).*
At 90 minutes the subjects (n=5) initiated deambulation. Values expressed as x ± SD.

		TIME (min)									
		−30	−15	0	10	15	20	30	60	90	120
PRA ng/ml/h	P	2.1 ± 0.6	2.1 ± 0.6	2.7 ± 0.6	2.7 ± 0.8	2.3 ± 0.7	2.5 ± 0.6	2.9 ± 0.7	2.0 ± 0.6	4.9 ± 0.6	5.7 ± 0.4
	M	2.6 ± 0.8	3.0 ± 0.2	3.1 ± 0.5	3.3 ± 0.5	3.2 ± 0.7	2.6 ± 0.4	3.0 ± 0.7	3.4 ± 0.3	4.7 ± 0.6	6.1 ± 0.7
PA ng/dl	P	3.0 ± 0.9	3.0 ± 1.3	2.6 ± 0.8	2.7 ± 1.1	2.0 ± 1.2	2.1 ± 0.8	2.6 ± 0.7	2.3 ± 1.1	6.0 ± 4.9	8.5 ± 4.5
	M	2.8 ± 0.7	2.8 ± 0.9	3.3 ± 1.5	8.3 ± 3.9	8.7 ± 4.6	8.5 ± 3.9	7.9 ± 4.2	6.7 ± 2.5	13.9 ± 9.9	14.9 ± 7.7
PRL ng/ml	P	8.5 ± 0.5	8.5 ± 0.5	7.7 ± 0.4	8.4 ± 0.8	6.6 ± 0.6	8.5 ± 2.8	8.4 ± 2.9	8.0 ± 2.2	8.0 ± 1.3	6.8 ± 1.2
	M	9.6 ± 1.0	7.9 ± 0.5	7.9 ± 0.6	82.2 ± 4.5	99.0 ± 12.7	98.7 ± 43.9	111.5 ± 20.5	77.7 ± 5.1	63.9 ± 8.6	54.4 ± 10.2
F μg/dl	P	11.7 ± 2.0	11.5 ± 3.5	9.9 ± 3.9	10.8 ± 4.9	9.4 ± 4.5	10.4 ± 4.3	9.2 ± 3.7	11.9 ± 5.3	11.9 ± 5.3	11.7 ± 4.3
	M	11.3 ± 3.2	11.0 ± 4.4	12.3 ± 5.9	10.5 ± 4.8	11.6 ± 3.9	9.9 ± 3.4	9.5 ± 2.4	9.9 ± 2.8	10.0 ± 3.5	10.7 ± 2.8
K mEq/l	P	4.1 ± 2.0	4.0 ± 0.4	3.9 ± 0.3	4.0 ± 0.3	3.9 ± 0.2	4.0 ± 0.2	4.0 ± 0.3	3.9 ± 0.2	4.0 ± 0.1	3.9 ± 0.2
	M	4.4 ± 0.1	4.4 ± 0.2	4.5 ± 0.3	4.4 ± 0.3	4.5 ± 0.1	4.5 ± 0.1	4.4 ± 0.2	4.5 ± 0.1	4.3 ± 0.2	4.4 ± 0.1

Table II. *Values of PRA, plasma aldosterone (PA), PRL, cortisol (F) and potassium (K) after seven days on a diet containing 20 mEq of sodium and 40 mEq of potassium daily obtained with the administration of placebo (P) or metoclopramide (M).*
At 90 minutes the subjects (n=5) initiated deambulation. Values expressed as x ± SD.

		TIME (min)									
		−30	−15	0	10	15	20	30	60	90	120
PRA ng/ml/h	P	5.1 ± 0.5	5.2 ± 1.7	5.1 ± 0.2	5.2 ± 0.9	5.1 ± 0.2	4.6 ± 0.3	4.3 ± 0.4	5.2 ± 0.6	8.0 ± 1.0	10.3 ± 0.8
	M	4.3 ± 0.5	4.5 ± 0.4	5.0 ± 0.2	5.1 ± 0.9	4.8 ± 0.7	4.0 ± 0.3	4.4 ± 0.3	5.0 ± 0.3	8.4 ± 1.0	10.6 ± 1.1
PA ng/dl	P	6.5 ± 1.4	7.2 ± 2.4	5.9 ± 1.3	6.8 ± 1.2	7.0 ± 1.4	6.2 ± 2.2	6.6 ± 2.6	6.9 ± 2.9	17.7 ± 10.6	27.7 ± 13.7
	M	5.9 ± 3.1	6.1 ± 2.6	5.8 ± 2.8	12.2 ± 4.7	17.1 ± 4.9	16.8 ± 5.7	15.2 ± 5.8	13.3 ± 4.5	21.2 ± 11.0	29.1 ± 11.6
PRL ng/ml	P	8.3 ± 0.7	7.7 ± 1.1	6.7 ± 1.2	6.6 ± 1.3	7.1 ± 0.9	6.5 ± 0.7	7.2 ± 1.1	7.7 ± 0.9	6.5 ± 0.5	6.9 ± 1.2
	M	9.0 ± 1.2	7.9±1.5	7.1 ± 1.0	84.6 ± 21.8	103.2 ± 23.9	121.1 ± 24.0	107.8 ± 16.1	89.8 ± 22.1	73.3 ± 23.7	69.9 ± 17.9
F μg/dl	P	11.1 ± 3.6	11.0 ± 3.7	10.0 ± 2.9	10.0 ± 3.2	9.6 ± 2.3	10.1 ± 2.8	9.8 ± 2.1	9.1 ± 2.1	10.4 ± 4.1	11.5 ± 4.8
	M	11.4 ± 2.7	11.2 ± 2.2	11.3 ± 2.9	12.0 ± 3.8	11.9 ± 3.9	9.4 ± 2.1	11.4 ± 3.6	10.4 ± 3.3	9.5 ± 3.1	9.1 ± 2.7
K mEq/l	P	4.0 ± 0.1	3.9 ± 0.1	4.1 ± 0.3	4.2 ± 0.5	4.1 ± 0.5	4.2 ± 0.3	4.3 ± 0.3	4.3 ± 0.4	4.3 ± 0.3	4.4 ± 0.3
	M	4.3 ± 0.2	4.3 ± 0.2	4.4 ± 0.2	4.4 ± 0.2	4.3 ± 0.2	4.2 ± 0.2	4.3 ± 0.2	4.2 ± 0.3	4.3 ± 0.2	4.4 ± 0.3

angiotensin II as well as of ACTH and potassium in the changes of plasma aldosterone in agreement with previous reports (2-4, 7).

The state of sodium balance influence the rate of synthesis and release of aldosterone by the adrenal gland in normal man. Restriction of sodium induces an increase of both plasma (10) and urinary levels (12) of aldosterone. The renin-angiotensin system has been purported to modulate the adrenal's response to variations in sodium intake (18). Sodium depletion also increases the sensitivity of the adrenal response to factors which act upon aldosterone secretion such as ACTH (13), potassium (5), and angiotensin II (6). Postural changes induce an increase in the plasma levels of aldosterone (10). These changes have been interpreted as mainly due to changes in renin-angiotensin system inducing increments in aldosterone secretion although a decrease in the metabolic clearance rate of aldosterone contributes to those findings (1). The present results show that the response of plasma aldosterone to metoclopramide administration behaves similarly in the two situations of sodium balance studied, although a higher increase of the aldosterone response was observed after sodium restriction. Our results are similar to those of SOWERS *et al.* (17). These authors postulate that in sodium restriction a more pronounced dopaminergic modulation of aldosterone secretion exists. It is our belief that this finding could merely reflect an increased adrenal sensitivity to metoclopramide administration secondary to sodium depletion similar to that seen with other factors which influence aldosterone secretion (5, 6, 13).

The present data show that the response of plasma aldosterone to metoclopramide administration is overridden by an increase in the endogenous production of angiotensin II although the increase of plasma aldosterone was lower after metoclopramide administration. A similar effect with the exogenous administration of angiotensin II has been previously reported (3).

Higher incremental responses of PRL have been observed in the present study, confirming the results of SOWERS *et al.* (17), during sodium depletion.

In conclusion, our results seem to indicate that the response of plasma aldosterone to metoclopramide administration is overridden by the endogenous production of angiotensin II and reflects changes after sodium depletion compatible with an increased adrenal sensitivity to the administration of the drug in the sodium depleted state.

Resumen

Se estudia la influencia del aumento de Angiotensina II endógena mediada por depleción de sodio y ortostatismo sobre los cambios de aldosterona inducidos por metoclopramida. Los resultados obtenidos demuestran que estos cambios son independientes de Angiotensina II, potasio y ACTH. La situación de balance de sodio modifica la respuesta de aldosterona a la metoclopramida, como ocurre con otros estímulos sobre dicha secreción.

References

1. BALIKIAN, H. M., BRODIE, A. H., DALE, S. L., MELBY, J. C. and TAIT, J. F.: *J. Clin. Endocrinol. Metab.*, **28**, 1616-1630, 1968.
2. CAREY, R. M.: *J. Clin. Endocrinol. Metab.*, **54**, 463-469, 1982.
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. COGHLAN, J. P., BLAIR-WEST, J. R., DENTON, D. A., FEI, D. T., FERNLEY, R. T., HARDY, K. J., MCDOUGALL, J. G., PUY, R., ROBINSON, P. M., SCOGGINS, B. A. and WRIGHT, R. D.: *J. Endocrinol.*, **81**, 55-67, 1979.
6. DOELKERS, W., BROW, J. J., FRASER, R., LEVER, A. F., MORTON, J. J., ROBERTSON, J. I. S.: *Circ. res.*, **34**, 69-77, 1974.
7. EDWARDS, C. R. W., AL-DUJAILI, E. A. S.,

BOSCARO, M., QUYYUMI, S., MIALL, P. A. and REES, L. H.: *Clin. Endocrinol.*, 13, 45-50, 1980.

8. EPSTEIN, M., LEVINSON, R., SANCHO, J., HABER, E. and RE, R.: *Circ. 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., ALCÁZAR, J. M., BARRIENTOS A., RODRÍGUEZ, F. J., RODICIO, J. L. and ORIOL, A.: *Endocrinología*, 25, 54-59, 1978.
11. HABER, R., KOERNER, T., PAGE, L. B., KLIMAN, B. and PURNODE, A.: *J. Clin. Endocrinol. Metab.*, 29, 1349-1354, 1969.
12. LUETSCHER, J. A. Jr. and AXELRAD, B. J.: *Proc. Soc. Exp. Biol. Med.*, 87, 650-656, 1954.
13. NEWTON, M. A. and LARAGH, J. H.: *J. Clin. Endocrinol. Metab.*, 28, 1006-1010, 1968.
14. NORBIATO, C., BEVILACQUA, M., RAGGI, V., MICOSSI, P. and MORONI, C.: *J. Clin. Endocrinol. Metab.*, 45, 1313-1316, 1977.
15. SANCHO, J. and HABER, E.: *J. Clin. Endocrinol. Metab.*, 47, 391-396, 1978.
16. SINHA, Y. N., SELBY, F. W., LEWIS, V. J. and VANDERLAAN, W. P.: *J. Clin. Endocrinol. Metab.*, 36, 509-514, 1974.
17. SOWERS, J. R., GOLUB, M. S., EGGENA, P. H. and CATANIA, R. A.: *J. Clin. Endocrinol. Metab.*, 54, 121-126, 1982.
18. WILLIAMS, G. H. and DLUHY, R. G.: *Am. J. Med.*, 53, 595-605, 1972.