J. steroid Biochem. Vol. 27, No. 4-6, pp. 947-951, 1987
Printed in Great Britain.

0022-4731/87 $3.00+0.00

Proceedings of the VII International Congress on Hormonal Steroids (Madrid, Spain, 1986)

PHARMACOLOGICAL INFLUENCES ON ALDOSTERONE SECRETION

RAFAEL GARCIA-ROBLES and LUIS M. RUILOPE

Service of Endocrinology, Hospital Ramon y Cajal and Service of Nephrology Hospital, 10 de Octubre, Madrid, Spain

Summary—Besides the classical modulators of aldosterone secretion, new factors influencing positively or negatively aldosterone secretion have been described. These new factors and the effect of related drugs constitutes the aim of this review. The effect of dopamine agonists and H_2-receptor antagonists on aldosterone secretion in normal volunteers as well as in different clinical situations characterized by an increased production of aldosterone opens a new field of investigation for the therapy of aldosterone secretion alterations.

INTRODUCTION

It is classically accepted that in man, aldosterone secretion is mainly controlled by the effects that angiotensin II ACTH and potassium exert on the adrenal gland [1]. However, in recent years new factors, contained in Table 1, have been implicated in the modulation of aldosterone secretion. The exact role of each one of these new regulators has not yet been defined but some of them have already been implicated in the pathogenesis of situations such as the hyperaldosteronism secondary to idiopathic hyperplasia. Furthermore, the use of drugs related to these new compounds opens up a wide field of investigation in the medical treatment of alterations of aldosterone secretion.

STIMULATING FACTORS

Besides angiotensin II, potassium and ACTH, some pituitary factors such as the aldosterone-stimulating factor (ASF) and propiomelanocortine (POMC) derivatives such as beta-lipotropine (β-LPH), beta-melanocyte-stimulating hormone (β-MSH) and gamma-melanocyte-stimulating hormone (γ-MSH) have been implicated in aldosterone biosynthesis. On the other hand, serotonine and histamine could also participate in the process of aldosterone secretion.

ASF is a 26,000 mol. wt glycoprotein found initially in human urine and later in plasma and anterior pituitary [2, 3]. ASF raises aldosterone secretion and blood pressure and the existence of a role in idiopathic hyperaldosteronism [3] has been postulated for this compound. Matsuoka *et al.* [4] have demonstrated that β-LPH and β-MSH stimulate aldosterone production in rat adrenal cells in the absence of changes in corticosterone. The recent description by Griffing *et al.* [5] of elevated levels of γ-MSH in patients with idiopathic aldosteronism compared with patients diagnosed of essential hypertension or primary aldosteronism secondary to adrenal adenoma also support the pathogenic role of pituitary factors in the control of aldosterone secretion.

Serotonin is synthesized from the aromatic amino acid L-tryptophan by a two-step process: first, hydroxylation, and second, decarboxylation [6]. Several renal, cardiovascular and endocrinological effects of serotonin, its precursor tryptophan and of serotonin antagonistic drugs have been described (see Table 2). In the 1950s several studies [7, 8] showed that the systemic administration of serotonin induced a diminution of urine volume and of sodium excretion both in animals and in hypertensive patients, probably as a consequence of a decreased renal blood flow. Later it has been demonstrated that serotonin and tryptophan are able to stimulate renin, aldosterone and cortisol [9–11]. In this way some investigators have suggested that the effects of serotonin could be mediated through an enhanced renin–angiotensin–aldosterone system [10]. In fact, the use of serotonin antagonists ameliorates the deranged renal blood flow and glomerular filtration rate in patients with a carcinoid syndrome [12]. Also, the diminution of the aldosterone response to metoclopramide induced by pizotifenum in normal

Table 1. Factors regulating aldosterone secretion

Stimulators
Angiotensin II
Potassium
Pituitary factors
ASF
POMC derivatives
ACTH
β-LPH
β-MSH
γ-MSH
Serotonin
Histamine?
Inhibitors
ANF
Dopamine
Low potassium levels

Table 2. Effects of serotonin, tryptophan and serotonin antagonists

Serotonin administration
↓Urinary volume [8]
↓Sodium excretion [8]
↑Renin secretion [10]
↑Aldosterone secretion [11]
Tryptophan administration
↑Renin, aldosterone and cortisol release [9]
Serotonin antagonists
Pizotifenum: ↓ aldosterone response to metoclopramide [13]
Ciproheptadine: ↓ aldosterone in idiopathic aldosteronism [14]

women [13] and the diminution of aldosterone levels obtained with ciproheptadine administration in idiopathic but not in primary aldosteronism [14] support the participation of serotonin in aldosterone regulation.

The response to ciproheptadine and the finding of elevated levels of γ-MSH in idiopathic hyperaldosteronism suggest that in this particular situation the pars intermedia of the pituitary gland, where the POMC derivatives are synthesized, could be under a positive serotoninergic and negative dopaminergic control and then contribute to the disregulation of aldosterone secretion [5].

Histamine, formed from decarboxylation of L-histidin, acts on the tissues through H1 and H2 specific receptors. In several tissues histamine raises prostaglandin secretion and some histamine effects can be modified by inhibition of prostaglandin synthesis [15, 16]. As prostaglandins stimulate renin secretion [17] it could be argued here that histamine could influence aldosterone secretion through variations of renin formation. In 1981, Edwards *et al.* [18] demonstrated that ranitidine, a histamine H2-receptor antagonist used in the management of peptic ulcer, significantly increased basal aldosterone production, and blocked the aldosterone response to angiotensin II but not to ACTH in isolated glomerulosa cells from the adrenal cortex of rats. In sodium-depleted volunteers we have described the existence of a blunted response of plasma aldosterone levels to deambulation after ranitidine administration [19].

We have recently performed a randomised double-blind study comparing the effect of ranitidine

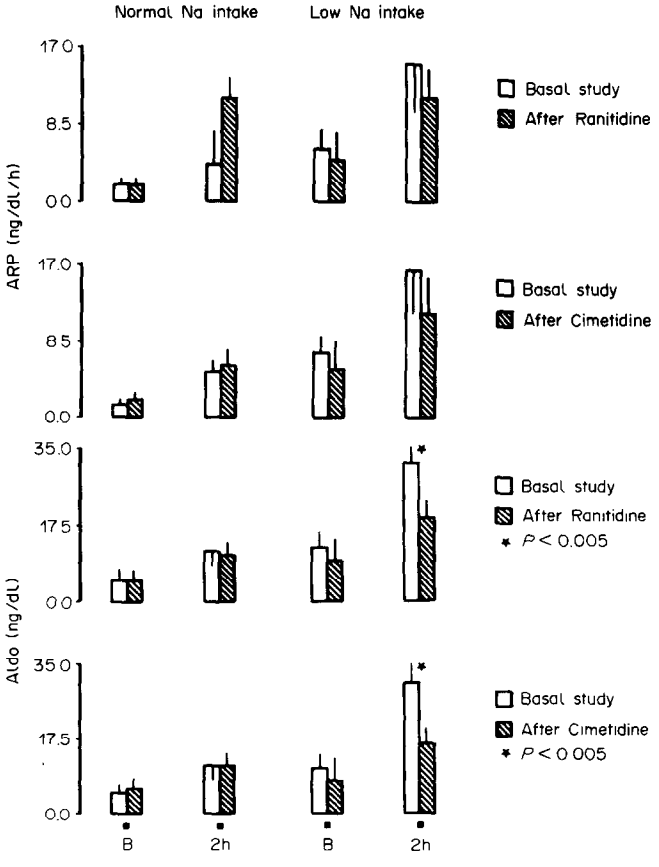

Fig. 1. Plasma renin activity and plasma aldosterone levels before and after ranitidine and cimetidine in normal volunteers. B—Basal, 2H—2 h deambulation. The subjects were studied while on a normal and low-sodium intake.

Table 3. Plasma prolactin (PRL) and urinary excretion of tetrahidroaldosterone (THA) and cortisol (F_U)

	Cimetidine		Ranitidine	
THA (μg/24 h)	Pre	After	Pre	After
Normal sodium	93.13	81.38	89.52	61.25
Restricted sodium	220.51	83.78*	223.17	97.88*
F_U(μg/24 h)				
Normal sodium	102.36	94.44	105.61	105.25
Restricted sodium	102.59	96.71	102.71	95.55

*$P < 0.05$ vs pre-treatment.

and cimetidine on aldosterone secretion in normotensive volunteers while on a normal and a low-sodium intake [20]. As can be seen in Fig. 1 the plasma levels of aldosterone did not show any change after the two H2-antagonists while on a normal sodium intake. Nevertheless, when sodium intake was low we confirmed our previous results with ranetidine and we found that cimetidine also induced a decrease of plasma aldosterone levels in response to ambulation. Furthermore, the measurement in the same volunteers of the 24-h urinary output of tetrahydroaldosterone, a reliable index of aldosterone secretion, (Table 3) showed that after sodium restriction both ranetidine and cimetidine inhibit the urinary output of tetrahydroaldosterone. The changes of aldosterone were not paralleled by similar changes of plasma renin activity (see Fig. 1) or in the urinary output of free cortisol (see Table 3). Plasma potassium did not exhibit any change throughout the study. All these findings point to the existence of a direct effect of ranetidine and cimetidine on aldosterone secretion in sodium depletion that is not mediated by angiotensin II, ACTH or potassium. The effect of H2-antagonist diminishing hepatic blood flow [21] could explain our findings of urine aldosterone but not those of plasma aldosterone, which should be the opposite.

INHIBITING FACTORS

A family of polypeptides, the atrial natriuretic peptides, with potent natriuretic and vasodilating activity has been recently isolated from the mammalian atrium [22]. These substances are able to inhibit aldosterone secretion both *in vivo*[23] and *in vitro*[24].

Besides ANF, potassium depletion is a well-established inhibitor of aldosterone production in experimental animals [24] and in man [25]. Calcium channel blockers at least *in vitro* decrease aldosterone production [26] but this effect has not been shown *in vivo*[27].

Along with ANF, low potassium levels and calcium channel blockers, dopamine, a neurotransmitter precursor of noradrenaline, is another aldosterone secretion inhibitor.

The possibility that dopamine could be implicated in aldosterone secretion was suggested by Edwards *et al.*[28] in 1975, who found that bromocriptine, a dopamine agonist, diminished the aldosterone response to furosemide in normal volunteers. The discovery by Norbiato *et al.*[29] that metoclopramide, a dopaminergic antagonist, raises plasma aldosterone levels reinforced the role of dopamine in aldosterone secretion.

Figure 2 contains our results obtained from studying the response of plasma aldosterone to metoclopramide administration in normotensive volunteers. As can be seen, the subjects were studied in two different situations of sodium balance—normal and low. In both situations, metoclopramide induced a significant increase of plasma aldosterone level that was higher in sodium depletion. A further increase of plasma aldosterone was observed after the 2 h of deambulation that followed the metoclopramide test and here again the response was, as expected, higher in sodium depletion. These results suggest, in accordance with Carey *et al.* [30], that dopamine might be an inhibitory mediator of the aldosterone response to angiotensin II.

The second half of the normal menstrual cycle is characterized by the presence of a relative hyperaldosteronism [31], and different responses of prolactin to the administration of TRH have been described in this particular situation [32]. The increase in aldosterone production and the responses

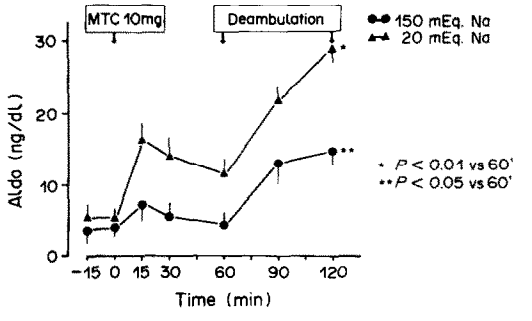

Fig. 2. Response of plasma aldosterone to metoclopramide (MTC) and deambulation in normal volunteers.

of prolactin could be interrelated through an alteration of the dopaminergic system.

Our studies in ovulating cycles have shown a different response of plasma aldosterone to the combined stimulus of deambulation and furosemide, with a higher response in the luteal phase (see Fig. 3). The administration of Lisuride, a dopaminergic agonist with D1 and D2 effects, induces a decrease in the aldosterone response to the same stimulus. These results point to the existence of a different dopaminergic tone in the second half of the normal menstrual cycle.

In clinical situations where a dissociation between aldosterone and plasma renin activity exists, such as low renin essential hypertension (LREH) the existence of dopaminergic system implications has been suggested [33]. Our results measuring hormones under dopaminergic control, such as thyroid-stimulating hormone and prolactin in response to TRH, in patients with LREH, have shown a significant difference between LREH, normoreninemic essential hypertension patients and volunteers [33]. These data point to a decreased dopaminergic tone that might be the link between a maintained aldosterone secretion and PRL hyper-response in LREH.

Another clinical situation we have studied has

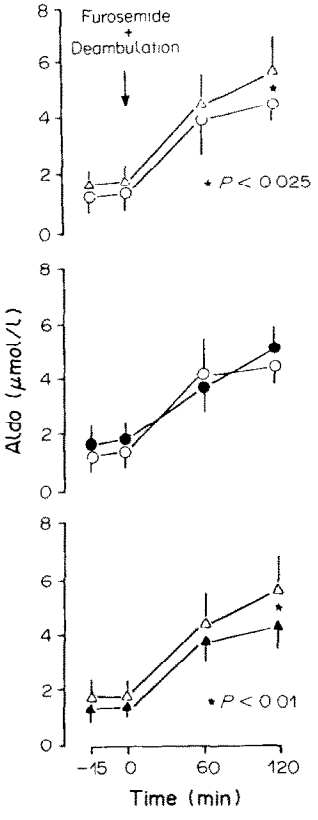

Fig. 3. Response of plasma and aldosterone to Furosemide and deambulation during the second half of the menstrual cycle. Effect of Lisuride administration (○, Follicular phase, ▲, luteal phase; ●, follicular plus Lisuride; △, luteal plus Lisuride.)

Table 4. Medical management of hyperaldosteronism*

Current therapies
Aldo antagonist
Spironolactone
Triamterene
Amiloride
Calcium channel blockers
Pituitary factor inhibitors
antiserotoninergic agents
Steroid biosynthesis inhibitors
Potential therapies
Dopamine agonists
ANF
ASF inhibitors
Opioid antagonists
Histamine antagonists?

*Hsueh W. A.: *Hypertension* **8** (1986) 76–82.

been the relative hyperaldosteronism found in patients with chronic renal failure (CRF), described more than two decades ago by Cope and Pearson [34]. In CRF the existence of a derangement of the dopaminergic control of other hormonal systems such as prolactin has been sought [35] and the hyperaldosteronism could be, at least partly, ascribed to a diminished dopaminergic tone. Our data [36], showing elevated basal values of aldosterone accompanied by lower levels of plasma renin activity and higher levels of prolactin in patients with terminal CRF on hemodialysis, are in agreement with previous descriptions. In these patients, the administration of a dopamine agonist(Lisuride) induced a decrease of plasma aldosterone levels [36]. These data favour the existence of a diminished dopaminergic tone in chronic renal failure.

From a practical point of view the medical management of hyperaldosteronism has clearly changed in recent years, as can be seen in Table 4. A few years ago only spironolactone seemed to be useful; nowadays, other diuretics such as triamterene and amiloride, calcium channel blockers, antiserotoninergic agents and new inhibitors of aldosterone biosynthesis are being used as current therapies. New potential therapies such as dopamine agonists, atrial natriuretic factor, aldosterone-stimulating factor inhibitors, opioid antagonists and perhaps histamine antagonists open a wide field for the investigation and treatment of different situations of hyperaldosteronism.

REFERENCES

1. Williams G. H. and Dluhy R. G.: Aldosterone biosynthesis: interrelationship of regulatory factors. *Am. J. Med.* **53** (1972) 595–605.
2. Saito I., Bravo E. L., Fanella T., Sen S. and Bumpus M.: Steroidogenic characteristics of a new aldosterone-stimulating factor (ASF) isolated from normal human urine. *Hypertension* **3** (1981) 300–305.
3. Carey R. M., Sen S., Dolan L. M., Malchoff C. D. and Bumpus F. M.: Idiopathic hyperaldosteronism: a pos-

sible role for aldosterone stimulating factor. *New Engl. J. Med.* **311** (1984) 94–100.
4. Matsouka H., Mulrow P. F. and Franco-Saez R.: Effects of b-lipotropin and b-lipotropin-derived peptides on aldosterone production in the rat adrenal gland. *J. clin. Invest.* **68** (1981) 725–729.
5. Griffing G. T., Bevelowitz B., Hudson M., Salzman R., Manson J. A. E., Aurrechia S. and Melby J.C.: Plasma immunoreactive gammamelaciotropin in patients with idiopathic hyperaldosteronism, aldosterone-producing adenomas and essential hypertension. *J. clin. Invest.* **76** (1985) 163–169.
6. Bosin T. R.: Serotonin metabolism. In *Serotonin in Health and Disease* (Edited by W. E. Essman), S.P. Medical and Scientific Books, New York, Vol. 4 (1978) pp. 181–300.
7. Barac G.: Recherche sur la brulure 5-hydroxytrypptamine et elimination renale du chlore chez le chien. *C.r. Soc. biol., Paris* **149** (1955) 1523–1525.
8. Hollander W. and Michelson A. L.: The effects of serotonin and serotonins in hypertensive man. *J. clin. Invest.* **35** (1956) 712–717.
9. Modlinger R. S., Chonmuller J. M. and Arora S. R.: Stimulation of aldosterone renin and cortisol by tryptophan. *J. clin. Endocr. Metab.* **48** (1979) 599–603.
10. Zimmermann M. and Handing W. F.: Pharmacological evidence that stimulation of central serotoninergic pathways increase renin secretion. *Neuroendocrinology* **30** (1980) 101–109.
11. Muller J. and Huber R.: Effects of sodium deficiency, potassium deficiency and uremia, upon the steroidogenic response of not adrenal tissue to serotonin, potassium ions and adrenocorticotropin. *Endocrinology* **85** (1969) 43–49.
12. Schneckloth R., Page J. M., Del Greco F. and Corcoran A. C.: Effects of serotonin antagonists in normal subjects and patients with carcinoid tumor. *Circulation* **16** (1957) 523–532.
13. Maestri E., Camellini L., Montanari R., Rossi G., Rossi G. P. and Nudi A.: Aldosterone regulation: a role for serotonin? In *The Adrenal Cycle and Hypertension* (Edited by F. Montero, E. G. Bigliori, I. W. Funder and B. A. Scroggins). Serono Symposia, Raven Press, New York, Vol. 27 (1985) 97–100.
14. Gross M. D., Grekin R. J., Gniadek T. C. and Villareal J. D.: Suppression of aldosterone by ciproheptadine in idiopathic aldosteronism. *New Engl. J. Med.* **305** (1981) 181–185.
15. Joan H., Sametz W.: Histamine induced release of arachidonic acid and of prostaglandins in the peripheral vascular bed. *Naunyn Schmiedebergs Archs. Pharmac.* **344** (1980) 183–190.
16. Baenziger N. L., Frece L. E. and Becherer P. R.: Histamine stimulates protacyclin synthesis in cultured human umbilical vein endothelial cells. *Biochem. biophys. Res. Commun.* **92** (1980) 1439–1440.
17. Dunn N. J.: Renal prostaglandins. In *Contemporary Nephrology* (Edited by S. Klar and S. G. Massry). Plenum Press, New York, Vol. 1 (1981) pp. 123–164.
18. Edwards C. R. W., Yeo T., Delatala G., Al Dujaili E. A. S., Boscaro M. and Besser G. M.: *In vitro* studies on the effects of ranitidine in isolated anterior pituitary and adrenal cells. *Scand. J. Gastroent.* **16** (Suppl. 69) (1981) 75–77.
19. Sancho J. M., Garcia Robles R., Mancheño E., Paya C., Rodicio J. L. and Ruilope L. M.: Interference by ranitidine with aldosterone secretion *in vivo*. *Eur. J. Pharmac.* **27** (1984) 495–497.
20. Garcia Robles R., Ruilope L. M. and Tovar, M. B.: Unpublished data.
21. Feely J., Wilkinson G. R. and Wood A. J. J.: Reduction of liver blood flow and propranolol metabolism by cimetidine. *New Engl. J. Med.* **304** (1981) 692–695.
22. Debold A. K., Borenstein H. B., Veress A. T. and Sonnenberg H.: A rapid and potent natriuretic response to intravenous injection of atrial myocardial extracts in rats. *Life Sci.* **28** (1981) 89–94.
23. Atarashi K., Mulrow P. J. and Franco Saenz R.: Effect of atrial peptides on aldosterone production. *J. clin. Invest.* **76** (1985) 1807–1811.
24. Hulter N. H., Sebastian A., Sigala J. E., Licht J. H., Glynn R. D., Schambelan M. and Biglieri E. G.: Pathogenesis of renal hypercloremic acidosis resulting from dietary potassium restriction in the dog: role of aldosterone *Am. J. Physiol.* **283** (1980) F79–F91.
25. Canon P. J., Ames R. P. and Laragh J. H.: Relation between potassium balance and aldosterone secretion in normal subjects and in patients with hypertensive or renal tubular disease. *J. clin. Invest.* **45** (1966) 865–879.
26. Capponi A. M., Lew P. D., Jornot L. and Vallotton M. A.: Correlation between cytosolic free Ca^{2+} and aldosterone production in bovine adrenal glomerulone cells. *J. biol. Chem.* **259** (1984) 8863–8869.
27. Ruilope L. M. and Garcia-Robles, R.: Unpublished data.
28. Edwards C. R. W., Miall P. A., Hanker J. P., Thorner M. O., Al-Dujaili E. A. S. and Besser G. M.: Inhibition of plasma aldosterone response to furosemide by bromocriptine. *Lancet* **II** (1975) 903–905.
29. Norbiato G., Bevilacqua M., Raggi V., Micossi P. and Morani C.: Metoclopramide increases plasma aldosterone in man. *J. clin. Endocr. Metab.* **45** (1977) 1313–1316.
30. Carey R. M. and Drake C. R.: Dopamine selectively inhibits aldosterone responses to angiotensin II in humans. *Hypertension* **8** (1986) 399–406.
31. Garcia Robles R., Ruilope L., Rodriguez F., Mancheño E., Rodicio J. L. and Oriol Boch A.: Role of sex and age on plasma aldosterone levels in normal subjects. *Acta endocr., Copenh.* (Suppl. 1) (1975) 199–200.
32. Boyd III A. E. and Sanchez Franco F.: Changes in the prolactin responses to tyroptrophin-releasing hormone (THR) during the menstrual cycle in normal women. *J. clin. Endocr. Metab.* **44** (1978) 985–989.
33. Garcia Robles R., Ruilope L. M. Hurtado A., Rodicio J. L. and Sancho J. M.: Dopaminergic control of prolactin and blood pressure. *Hypertension* **5** (1983) 155–156.
34. Cope C. L. and Pearsson J.: Aldosterone secretion in renal failure. *Clin. Sci.* **25** (1963) 331–341.
35. Sievertsen G. D., Lim V. S., Nakawatase C. and Frohman L. A.: Metabolic clearance and secretion rates of human prolactin in normal subjects and in patients with chronic renal failure. *J. clin. Endocr. Metab.* **50** (1980) 846–852.
36. Garcia Robles R., Ruilope L. M., Tovar J., de Villa F., Mirand B., Prieto C., Parada J., Sancho J. and Rodicio J. L.: Dopamine control of aldosterone secretion in end stage renal failure. *Rev. esp. Fisiol.* **42** (1986) 257–264.