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Effects of Calcium Channel Blockers on Potassium Homeostasis*

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The known effects of calcium channel blockers on various aspects of potassium homeostasis are reviewed. Regulation of potassium homeostasis requires both renal and extrarenal handling mechanisms. Signaling by calcium appears to mediate both of these. Calcium channels have been identified in adrenal glomerulosa cells, and cellular calcium entry has been demonstrated *in vitro* to be necessary for the synthesis and secretion of aldosterone. Calcium channel antagonists such as verapamil and nifedipine, at pharmacologic doses, can block aldosterone production. *In vivo,* however, only chronic administration of verapamil appears to attenuate aldosterone responsiveness to angiotensin II. Chronic administration of nifedipine does not have a dramatic effect on aldosterone production following potassium loading. Other studies have demonstrated improved extrarenal potassium disposal following treatment with calcium channel blocking agents. Clinically, there are no reports of either hyperkalemia or hypokalemia with the routine therapeutic use of these agents given alone. This review was prompted by the development of hyperkalemia in a patient with chronic renal failure following the initiation of therapy with the calcium channel blocker diltiazem; however, numerous other etiologies may also have contributed to the development of hyperkalemia in this case. Review of the data indicates that current evidence implicating this class of drugs in the pathogenesis of disordered potassium regulation remains equivocal.

INTRODUCTION

Calcium channel blockers are frequently prescribed in the management of hypertension and coronary artery disease. Although their use is generally well tolerated, numerous side effects have been described, most commonly hemodynamic abnormalities [1]. Metabolic disturbances have been only rarely described [12,13,14]. Recently, a patient was seen in consultation after developing severe hyperkalemia temporally related to the initiation of therapy with the calcium channel antagonist diltiazem. This condition prompted us to review the effects of calcium channel blockers on the pathogenesis of disorders of potassium regulation.

The patient was a 55-year-old male with a history of chronic renal failure and squamous cell carcinoma of the mouth, admitted for evaluation of a thyroid mass.

Abbreviations: ADH: antidiuretic hormone ADX: adrenalectomized (rat) AII: angiotensin II ANF: atrial natriuretic factor DOCA: deoxycorticosterone ICF: intracellular fluid compartment NPX: nephrectomized (rat) PRA: plasma renin activity PTH: parathormone PTX: parathyroidectomized (rat) TTKG: transtubular potassium gradient

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Surgical exploration revealed recurrent tumor. Pre-operatively, he was noted to have renal dysfunction with a baseline creatinine of 5 mg/dl and mild hyperkalemia with serum potassium concentrations 5.0–5.6 mEq/l. His post-operative course was uncomplicated except for an acute increase in the serum potassium concentration to 6.0 mEq/l one day after diltiazem was begun for treatment of hypertension. He was treated with sodium polystyrene sulfonate, and both enteral and intravenous sodium intake was increased. Daily potassium excretion was 24 mEq despite good urine output on a high sodium diet, and subsequent studies revealed that his serum aldosterone concentration was markedly depressed at <2.5 ng/dl. The transtubular potassium gradient (TTKG; see Appendix) was also markedly depressed at 2.3. Hyperkalemia did not readily resolve despite discontinuation of the calcium channel blockers but responded to pharmacologic concentrations of fludrocortisone, with a significant reduction in serum K^+ to 4.7 mEq/l and an increase in the TTKG to 5.2.

DISCUSSION

The etiology of the hyperkalemia in this case was most likely multifactorial. The initial high potassium values were associated with a significant reduction in glomerular filtration. Underlying hypoaldosteronism was subsequently documented. Despite these possible etiologies, the temporal relationship between the development of hyperkalemia and the addition of diltiazem made us suspect a role of this agent in the pathogenesis of this patient's disorder. This suspicion prompted a review of the effects of calcium channel blockers on potassium homeostasis.

Calcium Channel Blockers and Aldosterone Biosynthesis: In Vitro *Studies*

Aldosterone is synthesized in the adrenal cortex by glomerulosa cells and its production is stimulated by increases in plasma K^+ concentration, angiotensin II (AII), and ACTH. The effects of ACTH are mediated via cyclic AMP, whereas AII and hyperkalemia mediate aldosterone biosynthesis through cAMP-independent mechanisms.

The stimulation of aldosterone production or release by calcium has been intensively investigated. Numerous studies have examined the role of calcium on aldosterone production in response to the three major stimuli. Fakunding and Catt [2] have studied the *in vitro* effects of the calcium channel blockers lanthanum, a trivalent metal cation, and verapamil on aldosterone production in isolated dog and rat glomerulosa cells. When AII and ACTH were administered in maximally stimulating doses in the presence of lanthanum, there was a rapid and progressive inhibition of aldosterone production to both stimuli, although AII was more sensitive than ACTH to its effects. This inhibition was partially overcome when AII and ACTH concentrations were increased. Likewise, cAMP production was markedly diminished by calcium channel blockade. Similar results were obtained when hyperkalemic stimulation was employed, and, as with their previous experiments, this inhibition was again partially reversed by further increases in the extracellular K^+ concentration. Aldosterone production was similarly inhibited at verapamil concentrations of 10^{-6}M, with complete inhibition at approximately 10^{-4}M. This effect was dependent on the extracellular calcium concentration, and increasing the extracellular calcium concentration could partially overcome the inhibition at lower verapamil concentrations (Fig. 1).

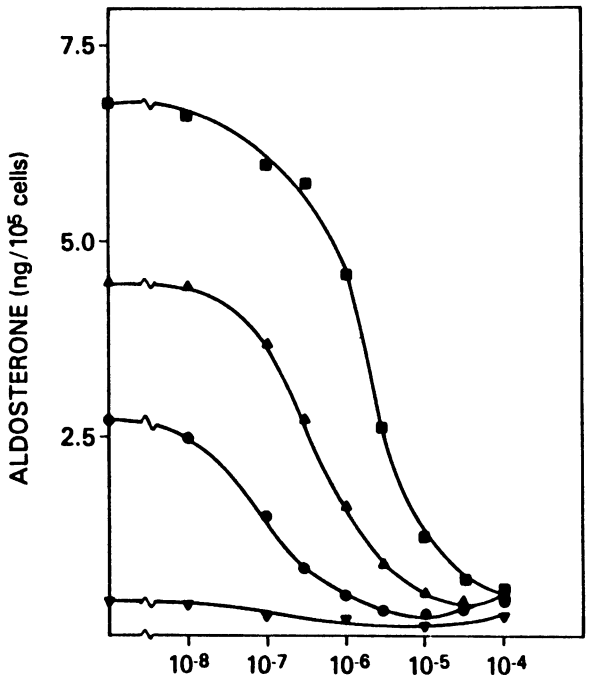

FIG. 1. The effect of extracellular calcium concentration on the inhibition by verapamil of aldosterone production stimulated by angiotensin II. Rat cells prepared in calcium-free medium (▼) or medium containing 0.1 mM (●), 0.4 mM (▲), or 1.2 mM (■) calcium were incubated with increasing concentrations of verapamil and 1 nM angiotensin II. (From [2]; reprinted with the permission of John L. Fakunding.)

Additional *in vitro* studies were performed by Foster et al. [3], investigating calcium uptake into bovine adrenal cells after stimulation by K^+ and AII. A progressive increase in aldosterone production was observed following AII or K^+ stimulation as a function of calcium concentration. Aldosterone production increased progressively, with maximal stimulation at a calcium concentration of 0.5 mM. Likewise, incubation with A23187, a divalent ionophore, was associated with a progressive increase in aldosterone production, whereas incubation with methoxyverapamil was associated with a progressive decline. They showed that AII and K^+ directly stimulate Ca uptake, and their results have been corroborated by others [4].

Patch clamp data using bovine adrenal glomerulosa cells have demonstrated the presence of two types of calcium channels, which are identified by their patterns of deactivation [5]. The "T-type" Ca channels activate slowly and inactivate rapidly in response to strong depolarizations. The other type, the "L-type" Ca channel, deactivates rapidly at more positive potentials. The T-type Ca channels were shown to be primarily responsible for mediating the response to AII and elevated K^+ concentrations. Activation of these channels by AII leads to calcium influx into cells, and nitrendipine was able to both block these channels and suppress aldosterone secretion in response to both stimuli. Molecular events relating cellular calcium entry and aldosterone biosynthesis are not yet clear. It is conceivable, however, that calcium may act as an intracellular mediator of enzyme activation.

Other potential mechanisms of inhibition of aldosterone synthesis by calcium channel blockers have only recently become understood (Fig. 2). Fakunding and Catt [2] have demonstrated that verapamil nonspecifically inhibits biosynthesis at a step preceding the formation of pregnenolone. Recently, however, Blanchouin-Emeric et al. [6] have shown that verapamil also inhibits the synthesis of aldosterone from

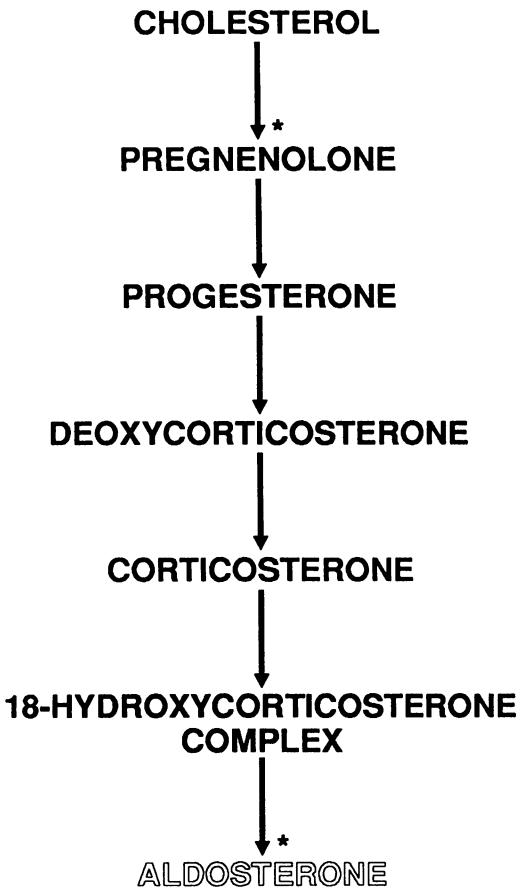

FIG. 2. Biosynthetic pathway for aldosterone synthesis. Asterisks indicate known steps for which inhibition by calcium channel blocking agents has been demonstrated [2,6].

18-hydroxycorticosterone in such a way that it has no effect on cellular respiration and without displacement of substrate from cytochrome P_{450} 11β, which is known to catalyze the conversion of 18-hydroxycorticosterone to aldosterone. Inhibition at this level occurred in the absence of the usual regulatory factors of aldosterone production and was independent of calcium. While these studies clearly demonstrate the dependence of aldosterone biosynthesis on calcium entry, the physiologic significance of these findings is unclear, since the concentrations of calcium channel blockers employed exceed those achieved *in vivo* by 1–2-log orders in magnitude [20–26].

Effects of Calcium Channel Blockers on Aldosterone Production: In Vivo *Studies*

In vivo studies in rats have investigated the role of calcium on plasma renin and aldosterone production [7,8,9]. Rats fed a normal NaCl diet showed augmentation of aldosterone production in response to high $CaCl_2$ intake, independent of changes in plasma renin activity. On a low NaCl diet, $CaCl_2$ ingestion was associated with a twofold rise in aldosterone. The effects of calcium ingestion on parathyroid hormone and vitamin D metabolism were not evaluated; thus, although direct effects of these on aldosterone metabolism cannot be excluded, these experiments appear to corroborate *in vitro* observations that Ca^{++} is a potent stimulus for aldosterone production.

Renal hemodynamic effects of calcium blockers have also been studied. Kotchen and Guthrie [7] showed that acute administration of verapamil, 4 μg/kg/minute to uni-nephrectomized dogs was associated with abrupt suppression of renin secretion but was unassociated with an effect on plasma aldosterone; however, chronic verapamil administration in rats did suppress plasma aldosterone levels to 35 percent of controls when rats were maintained on a low-salt diet.

Kotchen and Guthrie [7] have also studied the effects of acute and chronic verapamil administration on aldosterone responsiveness to graded intravenous infusions of AII and ACTH in normal subjects. Subjects were loaded intravenously with verapamil 8.5 mg and then maintained with a continuous infusion at 3.6 μg/kg/minute. There were no changes in blood pressure, heart rate, plasma renin activity (PRA), or plasma aldosterone. The pressor response to AII was prevented, and no effect was observed with regard to the incremental increase in plasma aldosterone in response to either AII or ACTH. Subsequently, the effects of chronic verapamil administration were evaluated. After five days of therapy with verapamil, 120 mg three times daily, both the pressor response and incremental rise in plasma aldosterone in response to AII were attenuated, although no significant differences were noted in response to ACTH. In neither experiment was serum K^+ studied.

Recently, Favre et al. [12] have studied the effects of nifedipine on aldosterone responsiveness to Na^+ depletion and K^+ loading in humans. Healthy volunteers were maintained on a 15 mmol Na^+, 100 mmol K^+ diet and treated with dexamethasone to suppress endogenous ACTH. Subjects were treated with either nifedipine 30 mg by mouth or placebo, and they were infused with KCl, 0.6 mmol/kg, over two hours. Baseline PRA was elevated in Na^+-depleted subjects and was significantly increased in nifedipine-treated patients. No changes were observed in plasma K^+ in either treatment group, and, despite that, a marked rise in plasma aldosterone was observed (Fig. 3). Nifedipine-treated subjects achieved aldosterone levels similar to that of controls, but the response was delayed.

Clinically, the effects of calcium channel blockers on aldosterone production at physiologic doses have been more difficult to demonstrate. Nadler et al. [10] used nifedipine to treat ten patients with primary aldosteronism due to either idiopathic hyperaldosteronism or adenomas. In this series, all patients showed a reduction in plasma aldosterone levels, improvement in blood pressure, and normalization of hyperkalemia. Bursztyn et al. [11] were, however, unable to demonstrate an improvement in plasma aldosterone or hyperkalemia following similar treatment in two patients with hyperaldosteronism due to adrenal adenoma. Larger studies will be required to establish the efficacy of these agents in the treatment of hyperaldosteronism.

In order to help further elucidate the clinical effects of calcium channel blockers on serum K^+, Kelleher and Gillum retrospectively examined the blood chemistry values of 46 patients prior to and following initiation of nifedipine therapy [13]. Serum K^+ increased significantly from 4.2 to 4.5 mEq/l; eight subjects developed modest hyperkalemia (serum $K^+ > 5.0$ mEq/l). Further examination showed, however, that development of significant elevations in serum K^+ occurred only in those patients concomitantly taking propranolol. Subjects with diabetes mellitus, renal insufficiency, and obstructive uropathy as well as those receiving oral K^+, K-sparing diuretics, and non-steroidal anti-inflammatory drugs were excluded from analysis; these patients represent a subgroup of patients who may be more sensitive to the

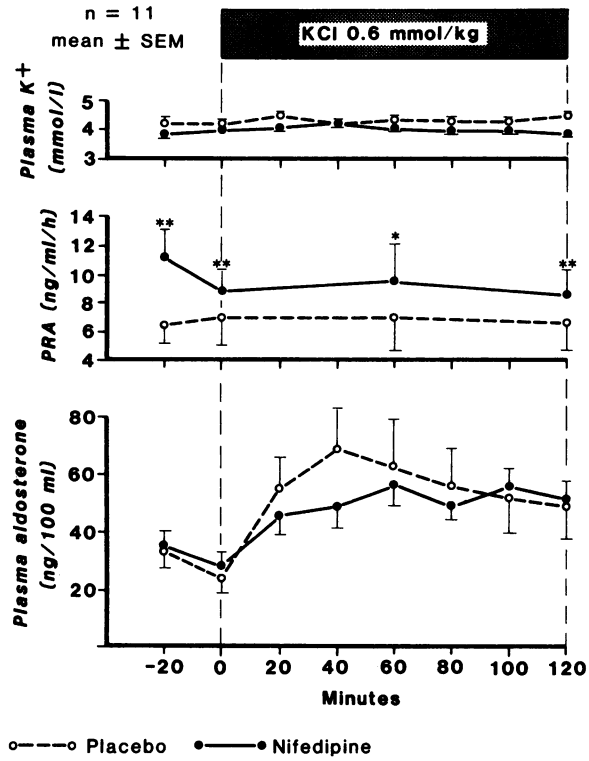

FIG. 3. Effect of a two-hour KCl intravenous infusion (0.6 mmol/kg in 5 percent glucose) on plasma potassium concentration, plasma renin activity, and plasma aldosterone levels, in 11 healthy subjects during sodium restriction. (From [12]; reprinted with the permission of Michel B. Vallotton.)

superimposition of other defects in K^+ excretion. That patients treated simultaneously with beta-blockers and calcium channel antagonists developed significant elevations in serum K^+ supports the notion that concomitant defects in K^+ handling may make one more susceptible to a second albeit mild defect. Further study of these higher-risk patients will be required to elucidate these issues. Hoyt [14] implicated diltiazem in the development of hyperkalemia in one patient taking this agent for management of hypertension. His claim has been disputed [15], as numerous factors, including advanced age, exogenous potassium ingestion, beta-adrenergic blocker ingestion, and mild renal insufficiency, may also have contributed.

Thus, it seems that although suppression of aldosterone production by calcium channel blockers is readily observed *in vitro,* the physiologic consequences *in vivo* are rare. Furthermore, their therapeutic benefits with regard to the treatment of hyperaldosteronism remain controversial and require further study. Adverse clinical sequelae have so far been most commonly observed in patients who are also using beta-adrenergic blockers. Thus, it is possible that further studies will reveal that calcium channel antagonists can contribute to hyperkalemia only in patients with a predisposition for this problem, such as diabetics and patients with underlying renal insufficiency. Since the inhibitory effects of calcium channel blockers on aldosterone production *in vitro* have, however, been demonstrated at drug concentrations of approximately 10^{-6}–10^{-7} M, which is far in excess of the serum drug concentrations of approximately 5×10^{-8} M achieved with the clinical use of these agents, it is unlikely that the effects will become clinically significant.

TABLE 1
Potential Effects of Calcium Channel Blockers on K Balance

1. *Data Demonstrating Effects Which Could Increase Serum K:*
   Suppression of aldosterone synthesis
   In vitro: Verapamil and nifedipine decrease AII, ACTH, and K-induced aldosterone biosynthesis [2,3,4,6]*
   Large non-clinical doses used
   In vivo: Chronic verapamil administration suppresses plasma aldosterone in salt-depleted rats [9]
   Diminished aldosterone responsiveness to acute K^+ load following chronic verapamil administration (blunting of time-response curve) [12]
   Decreased aldosterone levels and improvement of hyperkalemia in patients with hyperaldosteronism [10], reports not subsequently confirmed [11]
   Suppression of aldosterone synthesis may impair extrarenal K disposal in dialysis patients [16]
2. *Data Demonstrating Effects Which Could Reduce Serum K:*
   Enhancement of extrarenal K disposal in rats [17,19]

*References as listed

Effects of Calcium Channel Blockers on Extrarenal K^+ Handling

In addition to its well-known effect of modulating renal K^+ excretion, aldosterone may also play a role in mediating extrarenal K^+ disposal. Sugarman and Brown [16] examined the role of aldosterone in modulating extrarenal K^+ handling following 0.5 mEq/kg K^+ loads in anephric humans. The serum K^+ concentrations measured following KCl infusion were significantly lower after treatment with the synthetic mineralocorticoid deoxycorticosterone (DOCA, 10 mg intramuscularly daily) and were higher in patients treated with the mineralocorticoid antagonist spironolactone when compared to controls. The volume of distribution of K^+ was greater during DOCA administration than that in controls or spironolactone-treated subjects, and no changes were observed with regard to either fecal or salivary excretion. These results suggest that mineralocorticoids, at least at pharmacologic doses, may augment K^+ tolerance, presumably by affecting transcellular shifts.

The effects of calcium channel blockers on extrarenal K^+ handling have also been studied by Sugarman and Kahn [17]. Both verapamil and nifedipine were shown to blunt the rise in plasma K^+ following KCl infusion into nephrectomized (NPX), adrenalectomized (ADX) rats. Effects mediated by aldosterone, insulin, or the sympatho-adrenergic system were excluded. They hypothesized that K^+ translocation may relate to differences in regional blood flow or that diminished calcium influx may, in some fashion, be linked to impairment of K^+ efflux from the intracellular fluid compartment (ICF). Because parathormone (PTH) had previously been shown to enhance cellular calcium uptake, further studies were performed to assess its role in mediating extrarenal K^+ disposal [18]. Extrarenal K^+ handling was improved in nephrectomized (NPX), parathyroidectomized (PTX) rats, whereas this function was impaired following PTH administration. Soliman et al. [19] subsequently showed that verapamil improves K^+ disposal following PTH administration in adrenalectomized, NPX, PTX rats, suggesting that cellular calcium influx may directly mediate extrarenal K^+ disposal.

These data exemplify the complexity of effects of calcium channel blockade on

extrarenal K^+ homeostasis (Table 1). Whereas direct inhibition of aldosterone production by calcium channel blockers may impair translocation, impairment of cellular calcium entry directly promotes extrarenal K^+ disposal.

CONCLUSION

In summary, calcium channel blockers have two distinct effects on K^+ homeostasis (Table 1). Calcium is an important intracellular messenger for the synthesis and secretion of aldosterone in response to AII and K^+ and is necessary for the activity and production of cAMP in response to ACTH. Calcium channels have been identified in glomerulosa cells, and, *in vitro,* aldosterone production is blocked by calcium channel antagonists, at least at two sites. *In vivo,* however, only chronic administration of these compounds is associated with any appreciable suppression of aldosterone production. In humans, chronic verapamil administration attenuates the aldosterone responsiveness to AII administration but not to ACTH. In response to K^+ loading, nifedipine-treated, salt-deprived subjects were still able to achieve the same peak aldosterone levels, although there was a shift in the time-response curve to the left. Experimental studies have also demonstrated an improvement in extrarenal K^+ disposal with calcium channel blockers; however, these findings have not been confirmed clinically.

Initial reports demonstrating a reduction in aldosterone synthesis in patients with hyperaldosteronism have not been confirmed, and adverse clinical sequelae with the routine use of these drugs, with respect to K^+ homeostasis, has been rare. In addition to the potential ability of these agents to mediate extrarenal K^+ disposal, other factors are probably contributing, including the inability to achieve therapeutic drug levels with standard oral dosing to suppress aldosterone synthesis effectively *in vivo,* and the effects of other hormonal factors such as insulin, catecholamines, and atrial natriuretic factor (ANF) that also mediate K^+ tolerance.

The development of hyperkalemia in our patient had numerous potentially contributing etiologies, including mild volume contraction (leading to low distal tubular flow), chronic renal failure, and hypoaldosteronism. In view of the *in vivo* data detailed above, it is unlikely that the nifedipine or diltiazem contributed to his hyperkalemia. Furthermore, discontinuation of these calcium channel blocking agents did not readily improve his hyperkalemia. Thus, the potential role of these drugs in the development of hyperkalemia remains speculative.

APPENDIX

The TTKG has been described in detail by Halperin and others [27,28,29,30] as an index of K^+ secretory activity in the cortical collecting tubule. This concept has been employed clinically in order to differentiate renal from non-renal causes of hyperkalemia. Briefly, the TTKG has been defined as $U_K \times P_{osm}/U_{osm} \times P_K$ and relates the urinary K^+ to the serum K^+ concentrations corrected for medullary water absorption. Thus, it is a measure of the ability of the distal tubule to secrete K^+ against a gradient. In sodium-replete patients with intact antidiuretic hormone (ADH) responsiveness, a TTKG <4 has been associated with reduced mineralocorticoid bioactivity (i.e., either aldosterone deficiency or resistance to its effects). Regarding the patient described herein, the initial TTKG was 2.3, owing to both decreased absolute concentrations of aldosterone and to possible diminished aldosterone responsiveness related to significant renal insufficiency. These defects were partially overcome

by treatment with pharmacologic doses of fludrocortisone, which was associated with a significant increase in the TTKG.

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