Calcium Antagonists and Renal Hemodynamics: Implications for Renal Protection

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ABSTRACT

During the past decade, attention has focused on the effects of calcium antagonists on renal function. When administered in vitro to the isolated perfused kidney, calcium antagonists exhibit consistent actions permitting characterization of their renal effects. Calcium antagonists do not affect the vasodilated isolated perfused kidney, but they do dramatically alter the response of this preparation to vasoconstrictor agents. Our recent studies with the isolated perfused hydronephrotic rat kidney model, which permits visualization of afferent and efferent arterioles, have demonstrated that the augmentation of glomerular filtration rate observed in the isolated perfused kidney is attributable to preferential vasodilation of preglomerular vessels. Although the clinical implications of such observations have not been fully delineated, the results of recent studies indicate that calcium antagonists exert salutary effects on renal function in patients with impaired renal hemodynamics. Such disorders include radiocontrast-induced nephrotoxicity and transplant-associated acute renal insufficiency. It is apparent, however, that the effects of calcium antagonists on renal blood flow commend their use in the management of essential hypertension.

Key Words: Calcium antagonists, renal microcirculation, renal protection, nephrotoxicity, renal hemodynamics

Since the introduction of calcium antagonists over two decades ago, attention has focused on their beneficial effects in the management of symptomatic coronary artery disease and on their ability to lower blood pressure. During the past decade, it has become apparent that this class of drugs also has beneficial effects on the kidney (1-4). The purpose of this brief review is to consider the potential salutary therapeutic applications of calcium antagonists on renal hemodynamics and on renal excretory function.

I recently reviewed the pharmacologic effects of the calcium antagonists on renal hemodynamics (1-5). In brief, calcium antagonists do not affect the vasodilated isolated perfused kidney; however, they dramatically alter the response of the kidney to vasoconstrictor agents (1,2). Under conditions of in vitro perfusion (e.g., 80 to 100 mm Hg), the isolated rat kidney appears to possess little intrinsic vascular resistance. Accordingly, in the absence of exogenous vasoconstrictors, calcium antagonists exert no effect on renal perfusate flow or glomerular filtration rate (GFR) in this model (6,7). This attribute of the model facilitates pharmacologic investigation of the renal microvascular actions of vasoactive agents. Thus, in experimental settings where renal vascular tone is established by a specific vasoconstrictor stimulus, the effects of calcium antagonists can be directly examined.

In the presence of norepinephrine, calcium antagonists markedly augment GFR but produce only a modest improvement in renal plasma flow (2,3). The predominant influence of calcium antagonists on GFR suggests that these agents antagonize preglomerular vasoconstriction. In order to test this postulate directly, our laboratory developed a model of the isolated perfused hydronephrotic kidney, which facilitates direct observations of the renal microvasculature under defined in vitro conditions (8).

This technique has been previously detailed (2,8). In brief, unilateral hydronephrosis was induced in donor animals by unilateral ureteral ligation. After 8 to 10 wk, renal tubular atrophy had progressed to a stage that allowed microscopic visualization of the renal microvessels (9). At this point, the hydronephrotic kidneys were excised and studied by using a modification of the isolated perfusion technique previously described by our laboratory (10,11). The perfused kidney was excised and placed on the stage of an inverted microscope (Nikon, model K), modified to accommodate a heated chamber equipped with a thin glass viewing port on the bottom surface (Figure 1).

Recent studies with this model have demonstrated that the above-mentioned augmentation of GFR is attributable to a preferential vasodilation of preglomerular vessels (2-4). We therefore used the model
to assess the interaction of the endothelin and calcium antagonists on the renal microcirculation (12) as depicted in Figures 2 and 3.

ENDOTHELIN AND THE RENAL MICROCIRCULATION

Endothelin is a recently characterized, 21-amino acid peptide synthesized by cultured vascular endothelial cells (13,14) that is a potent renal vasoconstrictor (12,15-17). Although at present the physiologic and pathophysiologic roles of endothelin are largely speculative, this peptide appears to represent a normal gene product of endothelial cells (13,14). It has been proposed that elevated circulating levels of endothelin may play a pathophysiologic role in conditions such as hypertension (13), cyclosporine-induced nephrotoxicity (18), and acute renal failure (19).

When infused into anesthetized rats, endothelin decreases the renal blood flow and the glomerular ultrafiltration coefficient even before systemic blood pressure increases (17). We have conducted studies with both the isolated perfused kidney and the isolated perfused hydronephrotic kidney to further elucidate the effects of endothelin on the renal microcirculation (12). Our results indicate that endothelin elicits marked vasoconstriction in the isolated perfused kidney and that it profoundly decreases GFR in that same preparation (12). Furthermore, the findings of parallel studies in the isolated perfused hy-
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Dronephrotic kidney indicate endothelin is a potent real vasoconstrictor acting predominantly on the afferent arteriole (Figure 2). Endothelin elicited significant decreases in afferent arteriolar diameter at concentrations as low as 0.01 nM (12). Its effect on the afferent arteriole is in accord with its potent ability to decrease GFR.

Nifedipine reversed both the endothelin-induced afferent arteriolar vasoconstriction and the endothelin-induced decrement in GFR (Figure 3) (12). However, the modest afferent arteriolar vasoconstriction elicited by endothelin was refractory to reversal by the calcium antagonist.

Collectively, our studies indicate that calcium antagonists reverse afferent arteriolar vasoconstriction induced by widely divergent stimuli, including putative mediators of deranged renal hemodynamics such as endothelin. Such observations suggest that the activation of potential dependent calcium channels constitutes a final, common mechanism of afferent arteriolar vasoconstriction by diverse agonists. In contrast, the efferent arteriole appears to be highly refractory to the vasodilatory effects of calcium antagonists, indicating a remarkable intragran heterogeneity of mechanisms which activate smooth muscle within the renal microcirculation (2,12).

Although our studies have focused primarily on the actions of calcium antagonists at the level of the renal microcirculation, it should be emphasized that calcium antagonists may influence GFR via other intrarenal mechanisms (2,3), for example, by increasing Kf (1–3).

Calcium antagonists have additional properties that may contribute to their ability to afford renal protection under diverse experimental conditions and perhaps in clinical disorders (2,3). Some of the more prominent mechanisms postulated to mediate the renal protective actions of these agents are listed in Table 1. These include the ability of calcium antagonists to lessen injury by retarding renal growth (20), to attenuate mesangial entrapment of macromolecules (21–23), to counteract or attenuate the mitogenic effect of platelet-derived growth factor and platelet-activating factor (21,24), and to act as scavengers of toxic oxygen-free radicals.

The results of recent studies suggest that calcium antagonists can protect the kidney after reduction of renal mass (20,25,26). Dworkin and associates (20,27) have postulated that glomerular injury depends in great part, not solely on the pressure developed within the glomerular capillary, but on tension in the vessel wall. Tension appears to be influenced equally by glomerular pressure and vessel radius (Rg). Thus, if the glomerular capillary radius increases when kidneys hypertrophy, then wall tension rises on both a hemodynamic and a structural basis. Conversely, therapies that prevent hypertrophy could decrease tension by reducing Rg. Consistent with this hypothesis, Dworkin et al. (27) have recently reported that Rg was significantly increased in rats 8 wk after 1⁄3 nephrectomy. Administration of nifedipine was associated with a reduction in Rg sufficient to cause a decline in tension similar in magnitude to that produced by agents, such as angiotensin converting enzyme (ACE) inhibitors, that inhibit injury by reducing glomerular pressure (27).

As reviewed in detail elsewhere, additional salutary effects may relate to the ability of calcium antagonists to attenuate mesangial entrapment of macromolecules and to modulate platelet activating factor and platelet-derived growth factor (24,28,29,30).

Another intriguing possibility is that the renoprotective action of calcium antagonists may be attributable to their interaction with toxic free radicals. Several lines of evidence have indicated that, when stimulated by certain cytokines or by the terminal components of complement, mesangial cells can generate oxygen-free radicals, which in turn may propagate further glomerular damage (24,31). Because calcium antagonists can act as free radical scavengers, this property may contribute to their ability to counteract or attenuate glomerular damage.

### Table 1. Known and postulated mechanisms mediating the renal protective actions of calcium antagonists

<table>
<thead>
<tr>
<th>Mechanism</th>
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<tr>
<td>1. Reduce systemic blood pressure</td>
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<td>2. Reduce renal hypertrophy</td>
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<td>3. Modulate mesangial traffic of macromolecules</td>
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<td>4. Inhibit mitogenic effects of platelet-derived growth factor</td>
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<td>and of thrombin</td>
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<tr>
<td>5. Scavenge toxic oxygen-free radicals</td>
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<td>6. Reduce metabolic activity of remnant kidneys</td>
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<td>7. Ameliorate uremic nephrocalcinosis</td>
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<td>8. May block pressure-induced calcium entry</td>
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POSSIBLE APPLICATIONS FOR CALCIUM ANTAGONISTS IN RENAL DISEASE

On the basis of consideration of the pharmacologic effects of calcium antagonists on renal hemodynamics, it is evident that calcium antagonists have important potential applications in clinical medicine and nephrology. First, the striking effects of calcium antagonists on renal hemodynamics and renal sodium handling commend their use in the treatment of hypertension (32). Medications such as hydralazine that reduce peripheral vascular resistance directly have been used in antihypertensive therapy for many years, but their effectiveness is limited both by reactive stimulation of renal and hormonal responses that counteract their antihypertensive ac-
tions (Figure 4) (32) and by the induction of sodium retention. The consequent volume expansion results in pseudotolerance to the antihypertensive effects of hydralazine.

In contrast to direct-acting vasodilators such as hydralazine and minoxidil, calcium antagonists attenuate the expected adaptive changes in peripheral vascular resistance, heart rate, cardiac output, and extracellular fluid volume that eventually counteract the initial reduction in blood pressure. Calcium antagonists interfere with angiotensin II and alpha adrenergic-mediated vasoconstriction. They also counteract the sodium-retaining effects of decreased renal perfusion (2,4) and possibly decreased levels of natriuretic hormones (indicated by the symbol 11 in Figure 4).

Aside from their role in treating hypertension, the salutary effects of calcium antagonists on renal hemodynamics, in concert with their effects on cellular calcium metabolism, suggest a future role in managing certain types of acute renal insufficiency (4,5,33). Table 2 summarizes several such examples. Possibilities include the use of their ability to augment renal perfusion in clinical settings in which renal hemodynamics are compromised—for instance, the amelioration of radiocontrast-induced reductions in renal hemodynamics.

**PROTECTION AGAINST RADIOCONTRAST-INDUCED ACUTE RENAL FAILURE**

Studies in experimental models have demonstrated that calcium antagonism with either verapamil or diltiazem, or chelation of calcium with EGTA, attenuates both the magnitude and duration of radiocontrast-mediated intrarenal vasoconstriction (34). Recently, Neumayer et al. (35) carried out a prospective randomized double-blind study assessing the effects of 3 days of nitrendipine treatment on radiocontrast-induced nephrotoxicity. They interpreted their data as indicating that prophylactic administration of calcium antagonists ameliorates radiocontrast-induced renal dysfunction. Additional studies are presently being conducted to delineate the possible protective role of calcium antagonists in this clinical setting (36).

In an analogous manner, it has been proposed that calcium antagonists might exert a salutary effect in protecting against other experimental models of acute renal failure (4,33).

**ROLE IN TRANSPLANT-ASSOCIATED ACUTE RENAL FAILURE**

The prophylactic administration of calcium antagonists to donor kidneys ameliorates posttransplantation renal insufficiency. In a prospective randomized trial, Wagner et al. (37) evaluated the influence of diltiazem on the development of delayed graft function after transplantation of cadaveric kidneys. In this initial study, cadaver kidneys were harvested locally at the study center and diltiazem was added to Eurocollin solution (20 mg/L) at the time of donor nephrectomy. The graft recipient was given a preoperative bolus injection of diltiazem, followed by maintenance diltiazem therapy. In the control group, nine patients (41%) developed acute tubular necrosis compared with two patients (10%) in the diltiazem group (P < 0.05). In the control group, 3.5 ± 0.4 hemodialyses per patient were necessary compared with 0.6 ± 0.2 in the diltiazem group (P < 0.005).

Subsequently, Dawidson and Rooth (38) confirmed and extended these observations by using additional calcium antagonists. Collectively, these observations with diverse calcium antagonists indicate that the protection afforded is a class effect.

### Table 2. Current and potential applications of calcium antagonists in clinical medicine

| 1. Amelioration of renal insufficiency from |
| Radiocontrast agents |
| Cyclosporine nephrotoxicity |
| Aminoglycoside nephrotoxicity |
| Chemotherapy |
| 2. Organ preservation during harvesting of kidneys for transplantation |

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PROTECTION AGAINST CYCLOSPORINE NEPHROTOXICITY

Finally, calcium antagonists exert an important renoprotective effect in the setting of cyclosporine nephrotoxicity. Within the past several years, evidence indicating that calcium antagonists exert protective actions against cyclosporine nephrotoxicity has emerged (4,5,39,40). Although the exact mechanisms whereby calcium antagonists ameliorate cyclosporine nephrotoxicity are not clear, it is conceivable that they act by counteracting the effects of thromboxane and/or endothelin (41-43).

ROLE IN DIABETIC NEPHROPATHY

On the basis of several lines of clinical and experimental evidence, ACE inhibitors have been advocated as being advantageous in patients with diabetic nephropathy. On the other hand, investigation of the benefit of calcium antagonists in this setting is at an earlier stage. Studies by Brenner and associates (44) have provided a theoretical framework for assessing the salutary effects of ACE inhibition as a means of retarding the progression of renal failure in diabetic nephropathy. Those studies (45) and those of Myers and Meyer (46) have been interpreted as indicating that therapy directed at reducing the glomerular capillary pressure effectively retards the progressive loss of renal function in rats with diabetes mellitus. Subsequently, a number of investigators have extended these observations to the clinical arena and have demonstrated that ACE inhibition indeed is antiproteinuric and also appears to slow the rate of decline of GFR in diabetic patients (47,48). These findings have been marshalled to support the premise that ACE inhibitors may be uniquely advantageous in patients with diabetic nephropathy. Recently, a number of studies (49,50), including a rigorous, long-term prospective trial (51), have demonstrated that calcium antagonists may be equally efficacious in ameliorating diabetic proteinuria. At present, a number of well-controlled prospective randomized studies have been initiated to delineate further the relative efficacy and attributes of ACE inhibitors versus calcium antagonists in the diabetic patient with renal dysfunction (personal communication). We eagerly await their findings.

SUMMARY

Collectively, the above-cited observations of the renal vaso dilatory effects of calcium antagonists on the renal microcirculation commend their use in the management of hypertension. They constitute a means of lowering systemic blood pressure while preserving renal perfusion to this vital organ. Furthermore, the present observations raise the possibility that calcium antagonists may ameliorate acute renal insufficiency in clinical settings in patients at increased risk of developing acute renal failure. Although I have focused on the effects of calcium antagonists on renal hemodynamics, let me emphasize that the renal protective effects of these agents may also be attributable to their salutary effects on cellular and mitochondrial calcium (52,53). Additional investigation evaluating these possibilities, as well as the long-range consequences of the renal hemodynamic actions of calcium antagonists, is required.

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