Calcium Antagonists and the Kidney

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EPSTEIN, M. and LOUTZENHISER, RD. Calcium Antagonists and the Kidney. Tohoku J. Exp. Med., 1992, 166 (1), 123-134 — Recently, attention has focused on the effects of calcium antagonists on renal function. When administered in vitro to the isolated perfused kidney, calcium antagonist exhibit consistant 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 the kidney to vasoconstrictor agents. In the presence of norepinephrine, calcium antagonists markedly augment glomerular filtration rate but produce only a modest improvement in renal perfusion. Utilizing the isolated perfused hydronephrotic rat kidney model that permits direct visualization of afferent and efferent arterioles, we have demonstrated that this preferential augmentation of glomerular filtration rate is primarily attributable to a selective vasodilation of pre-glomerular vessels. Although the clinical implications of such observations are not yet clear, preliminary studies in experimental animal models indicate that calcium antagonists may exert salutary effects on renal function in clinical settings that are characterized by impaired renal hemodynamics. The possible benefits of calcium antagonists in ameliorating the development of renal dysfunction in patients in whom there is increased risk for the development of acute renal insufficiency remain to be evaluated. —— calcium antagonists; isolated perfused kidney; renal hemodynamics; renal microcirculation

One of the most important advances in medicine in the past two decades has been the development and introduction to medicine of calcium antagonists. Since their introduction, attention has focused on their beneficial effects on the management of symptomatic coronary artery disease, as well as their blood pressure-lowering effects (Epstein and Oster 1988). During the past ten years, there has been an increasing awareness that this class of drugs may exert beneficial effects on an additional target organ i.e. the kidney (Loutzenhiser and Epstein 1985, 1990). The purpose of this brief review is to consider their salutary effects on renal hemodynamics and renal excretory function.

A consideration of the earliest observations on the renal effects of calcium antagonists may provide insight as to why the dramatic effects of calcium antagonists on the kidney were appreciated only belatedly. When calcium antagonists
are administered in vivo, diverse effects on renal hemodynamics are observed. Experimental conditions, particularly factors that directly or indirectly alter basal renal vascular resistance, exert a marked influence on the renal hemodynamic response to calcium antagonists (Loutzenhiser and Epstein 1985, 1987b, 1988). When administered directly into the renal artery of anesthetized animals, calcium antagonists can be demonstrated to produce renal vasodilation and augment glomerular filtration rate (Abe et al. 1983; Dietz et al. 1983; Bell and Lindner 1984). On the other hand in conscious animals, oral or intravenous administrations of calcium antagonists have been reported to have no significant effects on renal hemodynamics (Yokoyama and Kaburagi 1983; Wallia et al. 1985).

Several mechanisms account for these divergent effects. Since calcium antagonists elicit vasodilation by countering the actions of vasoconstrictors, the underlying level of renal vasoconstriction constitutes a primary determinant of the magnitude of the vasodilatory response to calcium antagonists. Furthermore, since calcium antagonists interfere with excitation-contraction coupling of the vascular smooth muscle by blocking specific Ca\textsuperscript{2+} channels, and since the recruitment of calcium antagonist sensitive Ca\textsuperscript{2+} channels may differ with different vasoconstrictors, the renal hemodynamic response to calcium antagonists may vary, depending upon the prevailing factor influencing renal vascular tone (Loutzenhiser and Epstein 1985, 1987b, 1988).

Collectively, these considerations emphasize the necessity for evaluating the effects of calcium antagonists under conditions in which the factors influencing renal vascular resistance are carefully defined and controlled. The isolated perfused rat kidney offers distinct experimental advantages for such studies (Epstein et al. 1980; Loutzenhiser et al. 1982). First, renal perfusion pressure may be maintained constant, thus eliminating the reflex and autoregulatory responses to the hypotensive actions of calcium antagonists that occur in situ. Secondly, the influence of other extrarenal factors such as volume status, the level of vasoactive hormones, renal neural stimulation, and anesthetic agents can be eliminated by using the extracorporeally perfused kidney. Therefore, using this model, it is possible to evaluate accurately the modulation by calcium antagonists of the renal vasoconstriction elicited by different types of vasoconstrictor agents.

Because of the attributes of the isolated perfused kidney model enumerated above, we will now review our studies characterizing the effects of calcium antagonists on the vasoconstrictor responses using this model. Such studies furnish a basis for defining the renal hemodynamic effects of calcium antagonists.

**RESULTS AND DISCUSSION**

Figs. 1-3 illustrate the manner in which the isolated perfused kidney model has been utilized to delineate the effects of a calcium antagonist on renal hemodynamics. They summarize the ability of a dihydropyridine, nifedipine, to
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reverse the effects of norepinephrine on glomerular filtration rate (GFR). As depicted in Fig. 1, the administration of norepinephrine (3 × 10^{-7} M) caused renal perfusate flow to decrease from 37±2 ml/min/g to 20±4 ml/min/g and GFR to decrease from 0.8±0.1 ml/min/g to 0.2±0.1 ml/min/g. If no intervention is carried out, these effects of norepinephrine are sustained for the duration of the experiment.

Nifedipine caused a complete reversal of the norepinephrine-induced decrement in GFR while only partially reversing the norepinephrine-induced decrement in renal perfusate flow (RPF) (Fig. 2). In the representative study depicted in Fig. 2, an isolated perfused rat kidney was first infused with norepinephrine. The catecholamine was added to the artificial perfusion media at a concentration of 3 × 10^{-7} M and elicited a 55% decrease in GFR (i.e. from 0.50 to 0.14 ml/min/g). The addition of nifedipine produced a striking reversal of the decrement in GFR. Thus at 10^{-7} M, nifedipine returned GFR to pre-norepinephrine levels. In contrast, nifedipine was less effective in reversing the norepinephrine-induced decrease in renal plasma flow (RPF). Thus, RPF was increased only modestly by 10^{-7} M nifedipine. This preferential augmentation of GFR with a lesser reversal of RPF is characteristic of the response of the isolated perfused kidney to calcium

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Fig. 1. Alterations in perfusate flow (upper panel) and glomerular filtration rate (lower panel) of 8 unmanipulated kidneys (solid line) and 7 kidneys treated with 3 × 10^{-7} M NE (interrupted line). Results are mean ± s.e. Asterisks indicate significant differences compared to control (p < 0.05). Reproduced with permission from Loutzenhiser et al. (1985b).
antagonists during norepinephrine-induced vasoconstriction (Steele and Challoner-Hue 1984; Loutzenhiser and Epstein 1985; Loutzenhiser et al. 1985a, b).

This capability of dihydropyridines to augment GFR preferentially during norepinephrine-induced vasoconstriction in the isolated perfused rat kidney is a feature common to other organic calcium antagonists (Steele and Challoner-Hue 1984; Loutzenhiser and Epstein 1985; Loutzenhiser et al. 1985a, b), but not to all types of Ca entry blockers. This formulation is summarized in Fig. 3, which depicts the relative effects on GFR and RPF of nitrendipine (open circles), nisoldipine (squares) and diltiazem (triangles) during norepinephrine-induced vasoconstriction of isolated perfused rat kidneys. It is readily apparent that with each of these organic Ca antagonists, the effects on GFR predominate over the effects on RPF. Similar results have been reported with verapamil (Steele and Challoner-Hue 1984). In contrast, no preferential effect on GFR is observed when Ca entry is inhibited using inorganic manganese (closed circles, Fig. 3) (Loutzenhiser and Epstein 1985).

The preferential augmentation of GFR by calcium antagonists depends on the nature of the vasoconstrictor stimulus. When the renal vasculature is activated by potassium chloride or the thromboxane A2 mimetic U44069, GFR increases,
but in parallel with renal perfusate flow. This might indicate either that these two vasoconstrictors act only at the level of the afferent arteriole or that they activate the afferent and efferent arterioles by similar, calcium antagonist-sensitive mechanisms (Loutzenhiser and Epstein 1985, 1987a, 1988).

Of interest, we have observed a preferential augmentation of GFR only during conditions in which the renal vasculature is activated by either norepinephrine or angiotensin II. In each of these settings, a significant component of the reduction in perfusate flow is resistant to the influence of calcium antagonists. It is quite probable that preferential augmentation of GFR is due to dilation of the afferent arteriole, accompanied by preservation of efferent tone. This would suggest that the events coupling receptor occupation to vasoconstriction differ in the afferent and efferent arteriole. Fig. 4 summarizes the postulated effects of calcium antagonists on GFR and renal perfusate flow during vasoconstriction induced by norepinephrine, by a thromboxane mimetic, and by angiotensin II. As suggested by this schema, the differences in the relative sensitivity of the afferent and efferent arteriolar vessels to calcium antagonists in response to diverse agonists, can determine the resultant renal hemodynamic responses (Loutzenhiser and Epstein 1987a).
Direct visualization of the afferent and efferent arteriolar response

The predominant influence of calcium antagonists on GFR suggests that they antagonize the afferent arteriolar effects of agonists such as norepinephrine at the level of the afferent arteriole. To assess this possibility directly, we have recently modified the post-ischemic, hydronephrotic, rat kidney model (Steinhausen et al. 1983) to permit direct visualization of the response of the afferent arteriole to pharmacological interventions in an isolated perfused setting (Loutzenhiser et al. 1987, 1988). The afferent (AA) and efferent arteriole (EA) were visualized using videomicroscopy, and renal AA and EA diameters were measured by computer-assisted image analysis. Preliminary observations in vitro (Loutzenhiser et al. 1987b) and a recent in vivo study indeed support postulate. Fig. 5 depicts a representative study demonstrating the ability of nicardipine to vasodilate the afferent arteriole preferentially. The administration of angiotensin II (0.3 nM) elicited vasoconstriction of both the afferent and efferent arterioles. The subsequent administration of nicardipine in increasing doses from $10^{-9}$ to $10^{-7}$ M completely reversed the angiotensin II-induced contraction of the afferent arteriole, but did not alter the response of the efferent arteriole.

Similarly, we have observed that both diltiazem and nifedipine attenuate angiotensin II-induced afferent but not efferent arteriolar vasoconstriction (Loutzenhiser and Epstein 1990). The afferent arteriolar response to increased arteriolar tone is preferentially reduced by calcium antagonists.

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**Table 1. Proposed action on renal microvessels**

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Afferent tone</th>
<th>Efferent tone</th>
<th>Agonist alone</th>
<th>Agonist + calcium antagonist</th>
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</thead>
<tbody>
<tr>
<td>U44069 (Thromboxane)</td>
<td>↓</td>
<td>↓</td>
<td>Preferential decrease in GFR</td>
<td>Parallel increase in both GFR &amp; RPF</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>↓</td>
<td>↑</td>
<td>Decrease in both GFR &amp; RPF</td>
<td>Preferential augmentation of GFR</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>↓</td>
<td>↑</td>
<td>Preferential decrease in RPF</td>
<td>Exaggerated preferential augmentation of GFR</td>
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Fig. 4. A summary of the effects of calcium antagonists on glomerular filtration rate (GFR) and renal perfusate flow (RPF) during vasoconstriction induced by diverse agonists. Because each of the agonists differentially affect afferent and efferent arteriolar tone the blockade of afferent vasoconstriction by calcium antagonists results in divergent effects on GFR and RPF. Reproduced with permission from Loutzenhiser and Epstein (1987a).
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Lobar pressure is also attenuated by these agents (Loutzenhiser et al. 1987). Thus, these direct observations of the renal microvessels support the postulate that calcium antagonists augment GFR by exerting a preferential dilation of pre-glomerular vessels during angiotensin II-induced vasoconstriction. Although for reasons delineated above, our efforts have centered on examining the actions of calcium in defined in vitro settings, our findings are in agreement with observations obtained in vivo. Thus, calcium antagonists have been demonstrated to exert pronounced increases in GFR when administered during AII-induced vasoconstriction (Bell and Lindner 1984). Furthermore, Fleming et al. (1987) demonstrated that calcium antagonists exert a preferential dilation of pre-glomerular resistance vessels in the anesthetized rat with unilateral hydronephrosis, a model whose renal vascular tone has previously demonstrated to be AII-mediated (Steinhausen et al. 1986).

Although this article has focused primarily on the actions of calcium antagonists at the level of the afferent arteriole, it should be emphasized that there are
other possible intrarenal mechanisms whereby calcium antagonists might influence GFR (Fig. 6). As detailed elsewhere (Loutzenhiser and Epstein 1985, 1987a), it has been suggested that calcium antagonists may increase $K_f$. Although an inhibition of mesangial contractility is cited as a possible mechanism mediating this response, at this time the effects of calcium antagonists on mesangial contractility is a subject of continuing controversy. Studies in our laboratory (Fleming 1987) have suggested that the contractile response of isolated glomeruli to thromboxane is refractory to calcium antagonists. In contrast, others have observed that calcium antagonists partially attenuate mesangial contractility induced by angiotensin II and vasopressin (Kitamura et al. 1987; Venkatachalam and Kreisberg 1985). Voltage sensitive calcium influx has been documented in subcultured mesangial cells (Hassid et al. 1988; Takeda et al. 1988). Several investigators have suggested that intracellular calcium mobilization may be the primary modulator of mesangial cell contractility (Bonventre et al. 1986; Takeda et al. 1988). Additional studies are required to delineate the effects of calcium antagonists on mesangial contractility and to ascertain if podocyte function may also be modified by these agents.
Calcium antagonists also stimulate renin release (Churchill 1990) and, thus, would be expected to increase intrarenal AII formation. AII exerts multiple intrarenal actions that may be differentially inhibited by calcium antagonist, and this factor could influence the in vivo response to these agents. Finally, as discussed elsewhere (Loutzenhiser and Epstein 1985, 1987a, 1988b), calcium antagonists may inhibit tubular sodium reabsorption (Luft and Weinberger 1990) and indirectly affect GFR by influencing tubulo-glomerular feedback.

**Future Perspectives**

With the pharmacologic effects of the calcium antagonists on renal hemodynamics in mind, it is tempting to consider potential future applications for calcium antagonists in clinical medicine. Table 1 summarizes several such areas. The salutary effect of calcium antagonists on renal hemodynamics suggests that they may be particularly well suited as drugs in the management of hypertension. Furthermore, in contrast to the antinatriuretic tendency that characterizes traditional vasodilators, the ability of some calcium antagonists to be relatively natriuretic (or at least not sodium-retaining) (Luft and Weinberger 1990) commend their consideration in the antihypertensive armamentarium (Epstein and Oster 1988).

Additional possible future applications of calcium antagonists may include the utilization of their ability to augment renal perfusion in clinical settings in which renal hemodynamics are compromised. One such example might include the protective effect of calcium antagonists in ameliorating radiocontrast-induced reductions in renal hemodynamics. Several lines of evidence have demonstrated that the intrarenal administration of radiocontrast medium results in a prolonged vasoconstrictive response and reduction in GFR (Bakris and Burnett 1985; Loutzenhiser and Epstein 1985). Bakris and Burnett (1985) have demonstrated in animal experiments that calcium antagonism with several different calcium antagonists, or chelation of calcium with EGTA, attenuates the magnitude and duration of radiocontrast-mediated intrarenal vasoconstriction. These studies suggest that calcium constitutes an important mediator in the vasoconstrictive phase that attends radiocontrast medium administration. Future clinical trials

<table>
<thead>
<tr>
<th>Table 1. Future applications of calcium antagonists in clinical medicine$^a$</th>
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<tr>
<td>1. Amelioration of renal insufficiency from:</td>
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<tr>
<td>a. Radiocontrast agents</td>
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<tr>
<td>b. Aminoglycoside nephrotoxicity</td>
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<tr>
<td>c. Chemotherapy</td>
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<tr>
<td>d. Cyclosporin nephrotoxicity</td>
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<tr>
<td>2. Organ preservation during harvesting of kidneys for transplantation</td>
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$^a$Reproduced with permission from Epstein and Loutzenhiser (1990).
will assess if these agents exert a protective role in attenuating or preventing the adverse renal hemodynamic effects of radiocontrast agents.

In an analogous manner, it has been proposed that calcium antagonists might exert a salutary effect in protecting against acute renal failure. Lee et al. (1985) studied the effects of the calcium antagonist, diltiazem, on the natural history of glycerol-induced acute renal failure in rats. Animals pretreated with diltiazem for 3 days prior to glycerol administration developed a less severe renal failure syndrome. Treatment decreased the extent of tubular cell necrosis, and was associated with a more rapid histologic and functional recovery. Although data in man are lacking, future clinical trials may be considered to assess this possibility.

It has been proposed that the prophylactic administration of calcium antagonists to donor kidneys might serve to ameliorate post-transplantation renal insufficiency. Indeed, a recent preliminary report confirms such a formulation. Thus, in a recent clinical trial, Wagner et al. (1987) reported that diltiazem pretreatment significantly improved postgraft function of cadaver kidneys. Further studies to evaluate these possibilities as well as the long-range consequence of the renal hemodynamic actions of calcium antagonists are required.

Recently, attention has focused on the possible role of calcium antagonists in protecting against cyclosporine nephrotoxicity. Utilizing intravital fluorescent microscopy to monitor the linear velocity of blood cells as an estimate of subcapsular blood flow in mice, Dawidson and associates (Rooth et al. 1987), have demonstrated that cyclosporine markedly decreases subcapsular blood flow. Pretreatment with the calcium antagonists verapamil (0.3–0.4 mg/kg) or dihydropyridine (PN 200–110) prevent cyclosporine induced impairment of blood flow. In contrast, pretreatment with an alpha-blocking agent, phentolamine, did not prevent these effects. These interesting observations raise the possibility that calcium antagonists might be useful in ameliorating cyclosporine nephrotoxicity.

Collectively, these observations raise the possibility that calcium antagonists might have a role in ameliorating the course of acute renal insufficiency in clinical settings in which patients are at increased risk of developing acute renal failure.

Acknowledgments

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References


