Forum Minireview

Pathophysiological Significance of T-type Ca$^{2+}$ Channels: Role of T-type Ca$^{2+}$ Channels in Renal Microcirculation

Koichi Hayashi$^1$*, Shu Wakino$^1$, Koichiro Homma$^1$, Naoki Sugano$^1$, and Takao Saruta$^1$

$^1$Department of Internal Medicine, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

Received August 11, 2005; Accepted October 12, 2005

Abstract. Since conventional Ca$^{2+}$ antagonists, with predominant blockade of L-type voltage-dependent Ca$^{2+}$ channels, elicit preferential dilation of afferent arterioles, they might ostensibly aggravate glomerular hypertension. Recently, novel Ca$^{2+}$ antagonists, with inhibitory action on L/T-type Ca$^{2+}$ channels, have been reported to dilate both afferent and efferent arterioles. The present review attempted to characterize the renal action of these Ca$^{2+}$ antagonists and evaluated the consequences following the treatment with these agents. In contrast to conventional Ca$^{2+}$ antagonists (e.g., nifedipine), novel antagonists (e.g., benidipine, efonidipine) potently dilated afferent and efferent arterioles; their action on efferent arterioles appeared to be mediated by the T-type Ca$^{2+}$ channel blockade, probably through the inhibition of the intracellular Ca$^{2+}$ release. The comparison of the anti-proteinuric action in subtotally nephrectomized rats showed that efonidipine exerted more prominent action than nifedipine. Furthermore, Ca$^{2+}$ antagonists with T-type Ca$^{2+}$ inhibitory action inhibited renin/aldosterone release and proinflammatory process. Finally, patients with chronic renal disease given a 48-week efonidipine treatment showed reduced proteinuria, and this effect was seen even when mean arterial blood pressure failed to become less than 100 mmHg. Collectively, T-type Ca$^{2+}$ channel blockade provides beneficial action in renal injury. Various mechanisms serve to protect against renal injury, including systemic/glomerular hemodynamic action and non-hemodynamic mechanisms.

Keywords: renal microcirculation, voltage-dependent Ca$^{2+}$ channel, renal disease, efonidipine, mibefradil

Introduction

Voltage-dependent Ca$^{2+}$ channels, particularly of L-type channels, are widely distributed throughout the body, and they play a critical role in maintaining the vascular tone. In the kidney, the inhibition of L-type Ca$^{2+}$ channels with Ca$^{2+}$ antagonists including nifedipine, diltiazem, and nitrendipine elicits marked increases in glomerular filtration rate and renal blood flow. To the extent that these Ca$^{2+}$ antagonists block L-type Ca$^{2+}$ channels, these observations indicate substantial distribution of L-type Ca$^{2+}$ channels within the renal vascular bed. On the other hand, a growing body of evidence has recently been accumulated showing important roles of T-type Ca$^{2+}$ channels in various organs (1). In the cardiac sinus node, it has been demonstrated that T-type Ca$^{2+}$ channels participate in the generation of pacemaker potential. Furthermore, newly-developed Ca$^{2+}$ antagonists, including efonidipine and mibefradil, have been demonstrated to possess blocking activity on T-type as well as L-type Ca$^{2+}$ channels. Of particular interest, these antagonists exert renal microvascular action distinct from conventional Ca$^{2+}$ antagonists (e.g., nifedipine); these agents cause less increase in filtration fraction (2) and have more proteinuria-reducing action (3). Such renal action would prompt us to speculate that T-type Ca$^{2+}$ channels participate in the regulation of renal microvascular tone. In this review, we attempt to focus on the functional role of T-type Ca$^{2+}$ channels in the renal microcirculation. Furthermore, whether activation of T-type Ca$^{2+}$ channels is responsible for the development of renal injury is also discussed.
Characterization of renal microvessels

The kidney possesses multifaceted unique functions, including the regulation of water/electrolyte balance and glomerular filtration. Adjoining the glomerulus, both afferent and efferent arterioles exist and exhibit vasodilatation or vasoconstriction in response to various vasomotor stimuli. The responsiveness of these arterioles, however, should differ with respect to efficient function of glomerular filtration. Indeed, atrial natriuretic peptide causes afferent arteriolar dilation and efferent arteriolar constriction (4). Furthermore, elevated renal perfusion pressure (5) and endothelin (6) elicit predominant constriction of the afferent arteriole. L-type Ca\(^{2+}\) channels are distributed abundantly, and the channel subunits were expressed at juxtamedullary efferent arterioles. Similarly, Ono et al. (personal communication) have recently demonstrated that Ca\(_{\alpha_{1.2}}\) preferentially prevails at the rat afferent arteriole, whereas the efferent arteriole lacks this subunit. Collectively, available evidence indicates a preferential activity of L-type Ca\(^{2+}\) channels at the afferent, but not efferent, arteriole.

Role of T-type Ca\(^{2+}\) channels in renal microvessels

Unlike the conventional types of Ca\(^{2+}\) antagonists, novel types of these agents, including manidipine and efonidipine, are reported to dilate both afferent and efferent arterioles (8, 10). Tojo et al. (11) have reported that manidipine elicits both afferent and efferent arteriolar dilation in in vivo hydromephrotic kidney models, although the magnitude of the efferent arteriolar dilation is still less than that of the afferent arteriolar dilation. Using the microdissected renal arterioles, Arima et al. (12) also reported that manidipine caused efferent as well as afferent arteriolar dilation. Furthermore, Takabatake et al. (13) reported that in the rat micropuncture study, efonidipine reduces both pre- and postglomerular capillary resistance.

Although these observations suggest divergent action of Ca\(^{2+}\) antagonists on the efferent arteriole, there remains the possibility that different experimental conditions may affect the renal microvascular responsiveness to these agents. Nevertheless, we have demonstrated that several Ca\(^{2+}\) antagonists, including manidipine, nilvadipine, bendipidine, and efonidipine, cause substantial dilation of efferent arterioles in the isolated perfused rat hydromephrotic kidney (8, 10, 14). Since the traditional Ca\(^{2+}\) antagonists act on L-type voltage-dependent Ca\(^{2+}\) channels and these channels prevail predominantly at the afferent arteriole (7, 15), the effects on the efferent arteriole by these Ca\(^{2+}\) antagonists are most likely attributed to additional actions of these antagonists, but not due to the class effects of these agents.

As described, several Ca\(^{2+}\) antagonists elicit efferent as well as afferent arteriolar dilation (10 – 14). Recently, a pharmacological study has demonstrated that efonidipine possesses the blocking activity on T-type, as well as L-type, voltage-dependent Ca\(^{2+}\) channels (16). Indeed, T-type Ca\(^{2+}\) channels are closely associated with pacemaker potentials (17). In several microvasculature including mesenteric and cremaster arterioles, T-type Ca\(^{2+}\) channels are distributed abundantly, and the blockade of these channels by a selective T-type Ca\(^{2+}\) channel blocker, mibebradil, inhibits the vasoconstriction of these arterioles. In the renal microvasculature, Hansen et al. (9) have demonstrated that T-type Ca\(^{2+}\) channels prevail at juxtamedullary efferent arterioles, as well as afferent arterioles of superficial and juxtamedullary nephrons. Furthermore, Ono et al. (personal communication) have recently found the presence of a Ca\(_{\alpha_{3.1}}\) subunit (an \(\alpha_{3.1}\) subunit of T-type Ca\(^{2+}\) channels) at superficial efferent as well as afferent arterioles, with the use of in situ hybridization. Similarly, Nakamura et al. (18) found that mibebradil decreased both afferent and efferent arteriolar resistance in SHR kidneys, using the micropuncture technique. Recently, Ozawa et al. (19) have directly visualized an efferent arteriolar dilation by some Ca\(^{2+}\) antagonists that possess blocking activity on T-type Ca\(^{2+}\) channels. Both mibebradil and nickel chloride potently reverse the ANG II-induced constriction of the efferent arteriole in the isolated perfused rat hydromephrotic kidney model (Fig. 1). Furthermore, the intravital pencil-type CCD camera technique reveals that efonidipine and mibebradil provoke efferent as well as afferent arteriolar dilation in dog kidneys in vivo (2). Collectively, these novel findings strongly suggest a
critical role of T-type Ca$^{2+}$ channels in mediating the efferent arteriolar tone.

**Intracellular signaling mechanism of T-type Ca$^{2+}$ channels**

The mechanism whereby T-type Ca$^{2+}$ channel activity modifies the intracellular vasoconstrictor signaling pathway and thus dilates efferent arterioles remains undetermined. We previously demonstrated that ANG II-induced vasoconstriction is mediated by two main intracellular signaling pathways, protein kinase C (PKC) and inositol-1,4,5-trisphosphate (IP3)-induced intracellular Ca$^{2+}$ release (20, 21). In the ANG II-stimulated efferent arteriole, both PKC- and IP3-associated vasoconstrictor mechanisms are activated in an additive manner (20, 21). In this regard, mibefradil is reported to inhibit the PKC-mediated signaling pathway and prevent the vascular smooth muscle contraction in the vascular smooth muscle cell (22). Furthermore, Sipido et al. (23) reported that T-type channel activation facilitated Ca$^{2+}$ release from sarcoplasmic reticulum in cardiac myocytes. We therefore examined the interaction between these intracellular mechanisms and mibefradil-induced vasodilation. Thus, the PKC stimulation is relatively refractory to the vasodilator action of mibefradil (Fig. 2). Since staurosporine prevents the PKC-mediated constrictor mechanism, the major remaining vasoconstrictor mechanism of ANG II should be an IP3-mediated Ca$^{2+}$ release pathway (20, 21). Taken together, these observations are consistent with the view that that the IP3-mediated pathway constitutes an important target for the action of mibefradil during the ANG II-induced arteriolar constriction.

Additional mechanisms for the efferent arteriolar dilation by recently-developed Ca$^{2+}$ antagonists merit comment. It has been reported that T-type Ca$^{2+}$ channel activation stimulates renin release. Wagner et al. (25) have demonstrated that mibefradil suppresses renin release. This observation raises the possibility that T-type Ca$^{2+}$ channel blockade inhibits the ANG II production, and therefore would be anticipated to contribute in part to the efferent arteriolar vasodilation.

**Role of Ca$^{2+}$ antagonists in the progression of renal injury in animals**

The glomerular hemodynamic effects of traditional Ca$^{2+}$ antagonists suggest that these antagonists fail to correct glomerular hypertension in certain experimental conditions. Since the net effect of Ca$^{2+}$ antagonists on glomerular hemodynamics is determined by the balance between the reduction in afferent arteriolar resistance and the fall in systemic blood pressure, and the changes in these two factors may vary depending on the experi-
mental settings, magnitude of depressor activity, or types of Ca\textsuperscript{2+} antagonists used. For example, verapamil is reported to reduce proteinuria and protect against renal injury in remnant kidney models (26). In contrast, there have been several reports suggesting deleterious effects of dihydropyridine-class Ca\textsuperscript{2+} antagonists in renal diseases (27). Wenzel et al. (28) demonstrated that nitrendipine did actually increase proteinuria and glomerulosclerosis in the two kidney, one clip model of hypertension.

In contrast, the novel Ca\textsuperscript{2+} antagonists, acting on both afferent and efferent arterioles, may correct glomerular hypertension and could therefore exert salutary actions on the progression of renal injury. Indeed, Shudo et al. (29) reported that efondipine acutely decreased proteinuria in spontaneously hypertensive rats, whereas systemic blood pressure was only partially reduced. Additionally, it has recently been reported that mibefradil potently prevents the development of renal injury in SHR (18) and DOCA hypertensive rats (30).

Our previous studies demonstrated that 8-week-treatment with Ca\textsuperscript{2+} antagonists, including nifedipine and efondipine, showed a contrasting effect of these antagonists (3). Despite the same reduction in systemic blood pressure, efondipine markedly prevented the increase in proteinuria, whereas nifedipine did not reduce it. Furthermore, the histopathological changes and serum creatinine levels were also ameliorated by efondipine but not nifedipine. Of note, efondipine reduced proteinuria to the same level as enalapril, which causes both afferent and efferent arteriolar dilation. Thus, the renal protective effect of efondipine may be associated with the glomerular hemodynamic action of this agent, since efondipine is anticipated to reduce glomerular capillary pressure, as well as enalapril. In concert with the acute proteinuria-reducing effect, chronic effects of efondipine on proteinuria suggest a beneficial effect of this Ca\textsuperscript{2+} antagonist on glomerular capillary pressure, and
this could be mediated by a renal hemodynamic effect on the efferent arteriole.

Additionally, multiple mechanisms appear to contribute to the ability of the T-type Ca\(^{2+}\) antagonist to protect the kidney. It is reported that Ca\(^{2+}\) antagonists suppress mesangial cell proliferation by inhibiting activator protein-1 (AP-1) (31) and modulate gene transcriptions that are involved in proinflammatory changes (interleukin 1β and granulocyte/macrophage colony stimulating factors) (32). Efonidipine, a T-type Ca\(^{2+}\) antagonist, has also been shown to suppress the phorbol myristate acetate (PMA)-induced activation of nuclear factor kappa B (NFκB) in cultured human mesangial cells (33). Finally, Ca\(^{2+}\) antagonists could act as free radical scavengers (34).

Furthermore, the role of T-type Ca\(^{2+}\) channels in aldosterone release from adrenal gland has been reported. Rossier et al. (35) found that aldosterone release provoked by ANG II and KCl was inhibited by mibefradil but not by nicardipine, suggesting an important contribution of T-type Ca\(^{2+}\) channels to aldosterone release. Since aldosterone is reported to promote renal injury (36), the blockade of aldosterone release would be anticipated to exert salutary action on the progression of renal injury.

We have recently demonstrated that Rho kinase activation participates in the progression of renal injury in subtotal nephrectomized rats, a model of chronic renal failure (37). The inhibition of Rho kinase may therefore confer a benefit in the treatment of renal disease in addition to its hypotensive action. Of interest, in our preliminary study, we found that the Rho kinase inhibition by fasudil suppressed the ANG II-induced Rho

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**Fig. 3.** Schematic diagram illustrating the role of T-type Ca\(^{2+}\) channels in the development of renal injury. Both efonidipine and mibefradil exert beneficial action partly through hemodynamic mechanisms (hypotensive action and efferent arteriolar dilation). In addition, T-type Ca\(^{2+}\) channel blockade inhibits inflammatory process and Rho kinase activity, both of which subsequently lead to renal protection.

**Fig. 4.** Role of systemic blood pressure in the development of proteinuria in patients with proteinuria >1 g/day treated with angiotensin-converting enzyme inhibitors and efonidipine. ACE, angiotensin-converting enzyme. MAP, mean arterial pressure. *P<0.05 vs 0W. Modified from Ref. 38 with permission from the American Journal of Hypertension, Ltd. © 2003.
kinase activation, thus suggesting salutary action of this class of agent on renal disease (Fig. 3).

**Effect of efonidipine on the progression of renal injury in human renal disease**

It is well established that the inhibition of the renin-angiotensin system and the efferent arteriolar dilation constitutes a determinant of the renal protective action of angiotensin-converting enzyme (ACE) inhibitors in both experimental animals and humans. As described above, T-type Ca\(^{2+}\) channel inhibition shares this property with ACE inhibitors. We therefore compared the effect of efonidipine on the progression of renal disease with that of ACE inhibitors (38). Thus, 12 month-treatment with efonidipine in patients with non-diabetic renal disease elicited nearly the same magnitude of the reduction in proteinuria with that of ACE inhibitors (Fig. 4). Furthermore, creatinine clearance was well maintained in the efonidipine-treated group. In contrast, efonidipine provoked less adverse effects including less cough and hyperkalemia. Of note, even in patients in which mean systemic blood pressure did not achieve a level below 100 mmHg, proteinuria was significantly decreased (Fig. 4), suggesting an intrarenal action of this agent independent of the level of systemic blood pressure.

In conclusion, in both experimental and human renal disease, the T-type Ca\(^{2+}\) antagonists with dilatory activity on efferent arterioles would confer beneficial action on renal disease. It appears therefore that this action on glomerular microcirculation is anticipated to retard the progression of renal injury.

**Concluding remarks**

Characterization of the Ca\(^{2+}\) antagonist facilitates the renal action of this class of agent. It is now established that T-type Ca\(^{2+}\) antagonists exert renal protective action by ameliorating glomerular microcirculation with the property of vasodilator action on both afferent and efferent arterioles. Additionally, T-type Ca\(^{2+}\) antagonists may provide beneficial action by multiple mechanisms that act to suppress inflammatory processes and renin-angiotensin-aldosterone system (Table 1). Such multifaceted activity of T-type Ca\(^{2+}\) antagonists would be anticipated to protect against renal injury, and these drugs may be used more extensively in the treatment of hypertension with renal disease.

**References**


**Table 1. Possible mechanisms of T-type Ca\(^{2+}\) antagonist-induced renal protection**

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<td>Efferent arteriolar dilation</td>
<td>→ Correction of glomerular hypertension</td>
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Hemodynamic

Hypotensive action

Efferent arteriolar dilation → Correction of glomerular hypertension

Non-hemodynamic

Cell protection

Rho kinase inhibition

NFκB inhibition

Inhibition of leukocyte adhesion

Suppression of renin release

Suppression of aldosterone release

Suppression of sympathetic nervous system

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