Combined L-/T-Type Calcium Channel Blockers
Ready for Prime Time

Wei Ge, Jun Ren

Opening of the voltage-dependent Ca\(^{2+}\) channels permits influx of Ca\(^{2+}\) across the plasma membrane, triggering diverse physiological processes. These channels are widely distributed in the cardiovascular system, constituting the main route for Ca\(^{2+}\) entry essential for excitation and contraction. Ten unique \(\alpha_1\) subunits, grouped in 3 families (CaV1, CaV2, and CaV3), that encode the low-voltage–activated T-type and the high-voltage–activated L-, N-, P/Q- and R-type Ca\(^{2+}\) channels, have been identified.\(^1\)\(^2\) L-type Ca\(^{2+}\) channels are predominantly expressed in the hearts and peripheral vasculature and serve as the preferred molecular target of the initial Ca\(^{2+}\) channel antagonists in the treatment of hypertension.\(^3\)

Recently, a growing body of evidence has accumulated depicting important roles of T-type Ca\(^{2+}\) channels in the regulation of cardiovascular function, such as generation of pacemaker potential and regulation of arterial resistance.\(^3\)\(^4\) T-type Ca\(^{2+}\) channels are found in various cell types, including neurons, cardiomyocytes, vascular smooth muscle cells, and endocrine cells, where they participate in a variety of physiological processes, such as low-threshold Ca\(^{2+}\) spike generation, action potential firing, pacemaking, impulse conduction, maintenance of myogenic tone, cell proliferation, and hormone secretion.\(^1\) In addition to their predominant role in the regulation of vascular function, T-type Ca\(^{2+}\) channels are also involved in cardiomyocyte growth and survival.\(^3\)

T-type Ca\(^{2+}\) channel blockers are capable of interrupting certain pathological hypertrophic signaling pathways, including calcineurin-mediated nuclear factor of activated T cells–3 activation.\(^1\)

The importance of voltage-dependent Ca\(^{2+}\) channels is demonstrated by the clinical efficacy of Ca\(^{2+}\) channel blockers in certain disease conditions, as well as the widespread distribution and function of these channels.\(^1\) Three classes of chemically distinct L-type Ca\(^{2+}\) channel blockers have been widely used clinically depending on their biophysical and conformation-dependent interactions with the L-type Ca\(^{2+}\) channel. These 3 classes include the dihydropyridine, the phenylalkylamine (verapamil), and the benzothiazepine (diltiazem). Dihydropyridines are characterized by greater potency as vasodilators with less cardiodepressant properties than the other 2 types of Ca\(^{2+}\) channel blockers.

Although the clinical benefits of L-type Ca\(^{2+}\) channel blockers have been well defined, the clinical value of T-type Ca\(^{2+}\) channel blockade remains somewhat elusive. The newly developed dihydropyridine Ca\(^{2+}\) channel blockers, including manidipine, nilvadipine, benidipine, and efondipine, as well as the benzimidazole mibefradil, appear to possess vasodilatory properties other than blockade of L-type Ca\(^{2+}\) channels.\(^1\)\(^4\) These Ca\(^{2+}\) channel blockers may antagonize both L- and T-type Ca\(^{2+}\) channels, which possibly underlie their excellent clinical profiles, such as minimum reflex tachycardia and renal protection. Nonetheless, controversy still exists with regard to the precise role of T-type Ca\(^{2+}\) channels in the regulation of vascular tone. Mice deficient in CaV3.2 T-type Ca\(^{2+}\) channels display normal contractile responses and reduced acetylcholine-induced relaxation.\(^2\) Moreover, mibefradil exerts little effect on blood pressure or peripheral resistance in mice with conditional knockout of L-type Ca\(^{2+}\) channels.\(^5\) R(−)-enantiomer of efondipine, with a greater selectivity for T-type Ca\(^{2+}\) channels over efondipine, fails to alter blood pressure in hypertensive rats. The presence of T- but not L-type Ca\(^{2+}\) channel mRNA, was confirmed in microvessels with a diameter <40 \(\mu\)m.\(^3\) T-type Ca\(^{2+}\) channels are highly expressed in the microvasculature, including mesenteric and cremaster arterioles. Inhibition of these channels by mibefradil dampens vasoconstriction of these arterioles, although such effect seems to be attributed to L-type Ca\(^{2+}\) channel blockade.\(^5\)

In this issue of Hypertension, Ball et al.\(^6\) compared the inhibition of vascular contractile responses by L-type Ca\(^{2+}\) channel blockers (verapamil and nifedipine) and combined L-/T-type Ca\(^{2+}\) channel blockers (mibefradil and efondipine) in large conduit (rat aorta) and small (rat mesenteric and human subcutaneous) vessels. Although all 4 of the Ca\(^{2+}\) channel blockers inhibited contractile responses to a similar extent in large vessels, the combined L-/T-type Ca\(^{2+}\) channel blockers produced a significantly greater inhibition of contraction than L-type Ca\(^{2+}\) channel blockers alone in small vessels. Such a differential T-channel effect in microvessels was supported by a greater expression of T-type as opposed to L-type Ca\(^{2+}\) channels in microvessels but not large vessels. Given that microvessels play a pivotal role in the regulation of blood pressure, renal perfusion, and coronary blood flow, their findings implicate that T-type Ca\(^{2+}\) channels may contribute to the additional benefits of the combined L-/T-type Ca\(^{2+}\) blockers in treating renal and cardiovascular

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diseases, beyond their primary antihypertensive effects from blocking L-type Ca\(^{2+}\) channels.

Combined L-/T-type Ca\(^{2+}\) blockers have been demonstrated to be superior to L-type Ca\(^{2+}\) channel blockers in renal microcirculation.\(^2\) Inhibition of L-type Ca\(^{2+}\) channel causes dilation of afferent but not efferent arterioles, which potentially results in glomerular hypertension. This observation also indicates an intrarenal heterogeneity in the distribution of L-type Ca\(^{2+}\) channels. To the contrary, combined L-/T-type Ca\(^{2+}\) channel blockers, eg, mibebradil and efonidipine, dilate afferent and efferent arterioles, suggesting the presence of T-type Ca\(^{2+}\) channels in both arterioles, as well as a potential impact on intraglomerular pressure and renoprotection of combined L-/T-type Ca\(^{2+}\) blockers.\(^3\) However, other factors, such as the microheterogeneity of vascular beds and other types of Ca\(^{2+}\) influx, cannot be excluded.\(^3\) In addition, data from Ball et al\(^6\) provide further support for an important role for the T-type Ca\(^{2+}\) channel in the regulation of contractile responses in the microcirculation. Although the precise role of T-type Ca\(^{2+}\) channels in vascular beds remains to be determined, they may be associated with gene-activated cell replication and growth during pathological changes in the vasculature.\(^3\)

Combined L-/T-type Ca\(^{2+}\) channel blockers may possess greater efficacy than classical L-type Ca\(^{2+}\) channel blockers in the management of blood pressure and renal function. In a recent clinical investigation, >80% of patients displayed a significant reduction of blood pressure or achieved optimal blood pressure after a switch from amloidipine to benidipine. Moreover, the changeover improved urinary protein excretion and glomerular filtration rate, which correlated with reduced urinary protein.\(^7\) These observations are consistent with better antihypertensive and renoprotective effects of the combined L-/T-Ca\(^{2+}\) channel blockers. In addition, combined L-/T-type Ca\(^{2+}\) channel blockers possess a superior endothelial effect. The endothelial function index, a ratio of flow-mediated dilatation:nitroglycerin-mediated dilatation, was significantly increased in patients with essential hypertension after treatment of efonidipine but not nifedipine. Meanwhile, urinary excretion 8-hydroxy-2'-deoxyguanosine and serum malondialdehyde-modified low-density lipoprotein were decreased by efonidipine but not nifedipine, indicating a likely role of oxidative stress reduction in the efonidipine-induced improvement of vascular endothelial dysfunction.\(^8\) A schematic diagram is provided illustrating the benefit of combined L-/T-type Ca\(^{2+}\) channel blockers (Figure).

One common adverse effect of the L-type Ca\(^{2+}\) channel blockers is vasodilatory edema. Combined L-/T-type Ca\(^{2+}\) channel blockers, such as mibebradil, display antihypertensive efficacy similar to their predecessors with much less propensity of edema formation. It is believed that combined L-/T-type Ca\(^{2+}\) channel blockers equalize the hydrostatic pressure across the capillary bed through equal arteriolar and venular dilatation, thus reducing vasodialatory edema.\(^9\) Taken together, the incremental microcirculatory benefits of the combined L-/T-type Ca\(^{2+}\) channel blockers over the conventional L-type Ca\(^{2+}\) channel blockers are likely attributed to their additional T-type Ca\(^{2+}\) channel blocking properties and the increased presence of T-type Ca\(^{2+}\) channels in the microvasculature. However, adverse events associated with Ca\(^{2+}\) channel blockers, especially the high-profile withdrawal of mibebradil from the market because of unfavorable drug-drug interaction, have led to heated controversy over the safety, efficacy, and overall clinical merit of combined L-/T-type Ca\(^{2+}\) channel blockers. In general, these Ca\(^{2+}\) channel blockers, like other dihydropyridine Ca\(^{2+}\) channel blockers, demonstrate a more desirable profile when used as part of combination therapy.\(^10\) Additional study is warranted to quantify T- and L-type Ca\(^{2+}\) channels in the human vasculature and to assess the risk:benefit ratio of L-/T-type Ca\(^{2+}\) channel blockers. These efforts should foster novel approaches to discover potent and selective T-type Ca\(^{2+}\) channel modulators not only as potential drugs in the therapeutic armamentarium against cardiovascular disease but also as tools for a better understanding of the physiological roles of T-type Ca\(^{2+}\) channels.

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References

Image Content
A schematic diagram illustrating vascular regulatory effects of L-type and combined L-/T-type Ca\(^{2+}\) channel blockers in large and microvessels. The L-type Ca\(^{2+}\) channels (LCC) are predominantly expressed in large vessels, whereas T-type Ca\(^{2+}\) channels (TCC) prevail mainly in microvessels. The tissue heterogeneity of TCC and less undesirable effects may offer additional benefit for the combined L-/T-type Ca\(^{2+}\) channel blockers. The “T” end arrows denote inhibition.


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