Is Combined L- and T-Channel Blockade Better Than L-Channel Blockade in Therapy?

To the Editor:

Ball et al. elegantly identified functional differences in response to L- and T-Ca channel blockade based on vessel size. The authors suggest that combined L and T calcium channel blockers (CCBs) may have additional therapeutic benefits over conventional L-channel blockers. This hypothesis deserves further investigation.

Differential distribution of L- and T-type channels in the glomerular circulation is illustrated by a predominant dilatation of afferent arteriole by nifedipine, whereas efonidipine dilates both afferent and efferent arterioles. Efonidipine consistently reduces proteinuria in hypertensive patients with renal impairment. However, other clinical data show that cilnidipine, a L-N–type CCB, is renoprotective in diabetic nephropathy and that lacidipine, a L-type blocker, preserves renal graft function in cyclosporine-treated recipients.

Hemodynamic properties of CCBs are classically related to arteriolar vasodilation. Therapeutic regimens of CCBs evoke a reduction of blood pressure more pronounced in hypertensive than in normotensive patients. In spontaneously hypertensive rat vessels, this has been attributed to upregulation of CaL channels and the increase of their affinity for CCBs. The latter has been related to a higher proportion of inactivated CaL channels because of the lower resting membrane potential of spontaneously hypertensive rat vessels compared with Wistar-Kyoto vessels. The ratio of affinity between the open and inactivated states of CaL channels in arteries is varying among dihydropyridines, accounting for their vascular selectivity, an important parameter for their therapeutic effectiveness.

Other properties discussed elsewhere modulate CCB therapeutic efficacy, eg, interaction with the L-arginine-NO pathway, prevention of the overproduction of endothelin-1 in vessel walls, antioxidiant effect, and cardiovascular structural changes during long-term therapy.

Ball et al. studied the peak effect of endothelin-1. Prolonged exposure of various vessels, including isolated human coronary arteries, to threshold doses of endothelin-1 enhances the frequency opening of CaL channels, inducing the strengthening of vasoconstrictor action that is abolished by nanomolar concentrations of L-type CCBs such as nisoldipine. Analysis of the inhibition by various CCBs of the long-drawn-out effect of endothelin-1 in microvessels examined by Ball et al should enlarge information on the therapeutic mode of action of CCBs.

Disclosures

None.

Theophile Godfraind
Faculty of Medicine
Université Catholique de Louvain
Brussels, Belgium

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