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Lercanidipine and labedipinedilol-A play anti-inflammatory role through inhibition of lipopolysaccharide/interferon-γ-induced HMGB1 release and MMP-2, 9 activities in vascular smooth muscle cells

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Inflammation is an important molecular basis of atherosclerosis. Recent studies have shown that dihydropyridine calcium channel blockers (CCBs) can exert potent anti-inflammatory effects in models of vascular dysfunction. The purpose of the present study was to evaluate anti-inflammatory effects and mechanisms of lercanidipine and labedipinedilol-A, new generation dihydropyridine CCBs, in rat vascular smooth muscle cells (VSMCs) exposed to lipopolysaccharide (LPS) and interferon-γ (IFN-γ). MTT, Griess reagent, RT-PCR, ELISA, gelatin zymography, immunocytochemistry and Western blotting were employed. We found that lercanidipine and labedipinedilol-A attenuated production of NO, ROS, TNF-α and IL-1β from LPS/IFN-γ-stimulated VSMCs. In addition, they both diminished the LPS/IFN-γ-induced expression of iNOS protein and mRNA, with attenuation of HMGB1 cytosolic translocation and subsequent extracellular release. Furthermore, they down-regulated MMP-2/MMP-9 activities, while expression of tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), an inhibitor of MMP-9, was up-regulated. Finally, we found that lercanidipine and labedipinedilol-A inhibited the nuclear translocation of NF-κB and suppressed the phosphorylation of JNK, p38 MAPK and Akt. In conclusion, lercanidipine and labedipinedilol-A can exert their anti-inflammatory effects through suppression of NO, ROS, TNF-α and IL-1β through down-regulation of iNOS, MMP-2/MMP-9, and HMGB1, with inhibition of signaling transduction of MAPKs, Akt/IkB-α and NF-κB pathways. These findings implicate a valuable role of new generation dihydropyridine CCBs lercanidipine and labedipinedilol-A in the treatment of inflammatory vascular diseases.