Targeting Vascular Inflammaging with Amlodipine for Atherosclerosis Prevention

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I nitial and recent therapeutic interventions for the prevention of IHD are directed at these risk factors. Indeed, by intervening in these risk factors, especially dyslipidemia and hypertension, the incidence of cardiovascular disease and its mortality were dramatically reduced. In particular, angiotensin-converting enzyme inhibitors (ACEi), antihypertensive agents that act via RAS inhibition, have been proven to be powerful agents for reducing atherosclerosis in coronary arteries, thereby reducing the incidence of IHD.\(^2\)\(^3\) This was a plausible result because ACEi act on both the risk factor (hypertension) and its modifier (RAS) of atherosclerosis. However, one calcium channel blocker, amlodipine, once considered to be a mere vasodilator, was reported to reduce cardiovascular death as efficiently as the ACEi enalapril in patients with coronary disease and normal blood pressure (BP).\(^4\) The mechanism by which amlodipine affects IHD beyond BP lowering has long remained unclear.

In the current issue of International Heart Journal, Kayamori, et al. provided a novel mechanism of the anti-atherogenic effects of amlodipine treatment on a murine experimental model of atherosclerosis using apolipoprotein E-deficient (ApoE KO) mouse on high fat diet (HFD).\(^5\) The authors first focused on the components of amlodipine, consisting of two enantiomers, the S-enantiomer and R+ enantiomer. The former has L-type calcium channel blocking activity while the latter has 1,000-fold weaker activity.\(^6\) To determine the anti-atherogenic effects of amlodipine beyond vasodilation, ApoE KO mice on HFD were subjected to either vehicle, amlodipine (S-enantiomer plus R+ enantiomer), and R+ enantiomer, both at doses low enough so that no BP reduction was observed. Notwithstanding the unchanged BP or serum total cholesterol levels between the 3 groups, both amlodipine and R+ enantiomer treatments equally exhibited a significant reduction in aortic intimal formation, an early stage of atherosclerosis. Intriguingly, these anti-atherogenic effects of amlodipine and R+ enantiomer were positively correlated with the anti-senescence effects and anti-inflammatory effects, which were represented by the reduction of senescence-associated β-galactosidase (SA-β-gal) positive cell number and the reduction of pro-inflammatory cytokine gene expressions, respectively. Since these effects were observed without BP reduction, a hallmark of calcium channel blocker action by the S-enantiomer of amlodipine, the authors reasoned these effects derived from R+ enantiomer action. It has been reported that amlodipine releases nitric oxide (NO) independently of calcium blocking activity, and that NO serves as an anti-oxidant agent in blood vessels.\(^1\)\(^9\) Since p53, a critical inducer of senescence, is known to be induced by oxidative stress, the authors conducted an experiment to determine whether the anti-senescence effects of amlodipine and R+ enantiomer are attributable to the NO production and subsequent inhibition of oxidative stress-induced p53 activation. As expected, the p53 activity was induced by H₂O₂ treatment in VSMC in vitro and this p53 activation was significantly ameliorated by the treatment with amlodipine and R+ enantiomer, implying the anti-senescence effect of these drugs. These effects were then abolished by an NO synthase inhibitor, L-NAME, suggesting that the anti-senescence effects were attributable to their ability to release NO from VSMC, pos-
A proposed mechanism of the anti-atherogenic effects of amlodipine via NO-induced p53 inhibition. AT2R indicates angiotensin-2 receptor; and B2R, kinin B2 receptor. Amlodipine = S-enantiomer + R+ enantiomer

Figure.

Disclosures

Conflicts of interest: None.

References