ICoLA 2019
The 8th International Congress on Lipid &Atherosclerosis(ICoLA)
The 58th Conference of the Korean Society of Lipid & Atherosclerosis (KSoLA)
September 5(Thu.) ~ 7(Sat.), 2019, Conrad Hotel Seoul, Republic of Korea

ANTI-MALARIAL DRUGS REDUCE VASCULAR SMOOTH MUSCLE CELL PROLIFERATION VIA ACTIVATION OF AMPK AND INHIBITION OF SMAD3 SIGNALING

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Abstract

Objective: The aim of this study is to investigate the effect of anti-malarial drugs, chloroquine (CQ) and hydroxychloroquine (HCQ), on the inhibition of vascular smooth muscle cell (VSMC) proliferation both in vivo and in vitro.
Methods: Protein and mRNA levels were determined by western blot analysis and real-time reverse transcription-polymerase chain reaction in primary rat VSMCs treated with CQ and HCQ, respectively. Cell proliferation was measured by flow cytometry and cell counting. Mice carotid arteries were ligated and treated with CQ and HCQ every other day for 3 weeks. Pathological changes of carotid artery were visualized by both microscopy and fluorescence microscopy.
Results: Abnormal proliferation of VSMC is thought to play an important role in the pathogenesis of both atherosclerosis and restenosis. AMP-activated protein kinase (AMPK) plays a critical physiological role in the cardiovascular system. CQ and HCQ increase AMPK phosphorylation in VSMCs. CQ or HCQ decreased PDGF-induced VSMC proliferation and cell cycle progression in an AMPK-dependent manner. In addition, CQ and HCQ inhibit Smad3 phosphorylation and VSMC proliferation induced by TGFβ1. Moreover, CQ and HCQ diminished neointimal proliferation in a mouse model of carotid artery ligation-induced neointimal formation.
Conclusion: The results demonstrated that CQ and HCQ inhibit cell proliferation and cell cycle progression in VSMCs via AMPK-dependent signaling pathway. Carotid artery ligation-induced intima thickness was reduced in the mice arteries treated with CQ and HCQ, suggesting the implication of antimalarial drugs for atherosclerosis and restenosis.

Keywords

Chloroquine, hydroxychloroquine, vascular smooth muscle cell, AMPK, intimal formation