**METFORMIN ENHANCES T0901317-REDUCED ATHEROSCLEROSIS AND INHIBITS T0901317-INDUCED HYPERTRIGLYCERIDEMIA--A NEW STRATEGY FOR ATHEROSCLEROSIS TREATMENT**

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The progress on selective liver X receptor beta (LXRbeta) modulators which reduce atherosclerosis without lipogenic effect is limited. Metformin, a medicine used for diabetes treatment, activates AMPKƒÑ to enhance energy metabolism. In this study, we determined if co-treatment of metformin with LXR ligand (T0901317) can inhibit atherosclerosis while eliminating LXR-induced hypertriglyceridemia. ApoE deficient (apoE-/-) mice were fed a high fat diet (HFD) or HFD containing T0901317 or metformin alone or both for 16 weeks. T0901317 or metformin alone inhibited lesion development of en face aorta, sinus of aortic root and other parts of aorta while the combined T0901317 and metformin further reduced lesions. Structurally, the combined T0901317 and metformin increased the content of smooth muscle cells/collagen in fibrous caps while reducing necrotic cores and mineralization within lesions suggesting increased plaque stabilization. T0901317 alone resulted in development of fatty liver, activated hepatic lipogenesis, and increased activities of aminotransferases. However, these adverse effects were eliminated by metformin. Mechanistically, co-treatment of T0901317 and metformin reduced macrophage accumulation while activated expression of ABCA1 and ABCG1 in aortic root lesion areas, and inhibited foam cell formation in vivo. In macrophages, metformin had little effect on T0901317-induced LXRalpha and LXRbeta expression or nuclear translocation. In contrast, metformin moderately inhibited T0901317-induced hepatic LXRalpha or LXRbeta expression, and selectively reduced hepatic LXRalpha, but not LXRbeta, nuclear translocation. Therefore, metformin inhibited T0901317-activated expression of lipogenic genes, such as SREBP1, ACC1 and FASN, and phosphorylation of ACC1 which substantially reduces T0901317-induced hepatic lipid accumulation. In addition, metformin inhibited LXR-induced serum total-, LDL-, VLDL-cholesterol and triglycerides levels. Taken together, our study suggests that co-treatment of metformin and T0901317 might be a new strategy for atherosclerosis treatment without lipogenesis.