

Abstract

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Serine palmitoyltransferase (SPT) deficient mice absorb less cholesterol.

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BACKGROUND: Serine palmitoyltransferase (SPT) is the key enzyme for the biosynthesis of sphingolipids. It has been reported that oral administration of myriocin (an SPT inhibitor) decreases plasma sphingomyelin (SM) and cholesterol levels, and reduces atherosclerosis in apoE knockout (KO) mice.

METHODS AND RESULTS: We studied cholesterol absorption in myriocin-treated WT or apoE KO animals and found that, after myriocin treatment, the mice absorbed significantly less cholesterol than controls, with no observable pathological changes in the small intestine. More importantly, we found that heterozygous Sptlc1 (a subunit of SPT) KO mice also absorbed significantly less cholesterol than controls. To understand the mechanism, we measured protein levels of Niemann-Pick C1-like 1 (NPC1L1), ABCG5, and ABCA1, three key factors involved in intestinal cholesterol absorption. We found that NPC1L1 and ABCA1 were decreased, whereas ABCG5 was increased in the SPT deficient small intestine. SM levels on the apical membrane were also measured and they were significantly decreased in SPT deficient mice, compared with controls.

CONCLUSION: In conclusion, SPT deficiency might reduce intestinal cholesterol absorption by altering NPC1L1 and ABCG5 protein levels in the apical membranes of enterocytes through lowering apical membrane SM levels. This may be also true for ABCA1 which locates on basal membrane of enterocytes. Manipulation of SPT activity could thus provide a novel alternative treatment for dyslipidemia.

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