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Alpha-lipoic acid regulates the autophagy of vascular smooth muscle cells in diabetes by elevating hydrogen sulfide level.

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Abstract

Dysfunctional vascular smooth muscle (VSM) plays a vital role in the process of atherosclerosis in patients with type 2 diabetes mellitus (T2DM). Alpha-lipoic acid (ALA) can prevent the altered VSM induced by diabetes. However, the precise mechanism underlying the beneficial effect of ALA is not well understood. This study aimed to determine whether ALA ameliorates VSM function by elevating hydrogen sulfide (H_2S) level in diabetes and whether this effect is associated with regulation of autophagy of VSM cells (VSMCs). We found decreased serum H_2S levels in Chinese patients and rats with type 2 diabetes mellitus (T2DM). ALA treatment could increase H_2S level, which reduced the autophagy-related index and activation of the 5'-monophosphate-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) pathway, thereby protecting vascular function in rats with T2DM. Propargylglycine (PPG), a cystathionine-γ-lyase inhibitor, could weaken the ALA effect. In cultured VSMCs, high glucose level also reduced H_2S level, upregulated the autophagy-related index and activated the AMPK/mTOR pathway, which were reversed by concomitant application of sodium hydrosulfide (NaHS, an H_2S donor) or ALA. The protective effect of NaHS or ALA was attenuated by rapamycin (an autophagy activator), 5-amino-1-β-d-ribofuranosyl-imidazole-4-carboxamide (an AMPK activator) or PPG. In contrast, Compound C (an AMPK inhibitor) enhanced the effect of ALA or NaHS. ALA may have a protective effect on VSMCs in T2DM by elevating H_2S level and downregulating autophagy via the AMPK/mTOR pathway. This study provides a new target for addressing diabetic macroangiopathy.

KEYWORDS: Alpha-lipoic acid; Autophagy; Hydrogen sulfide; Type 2 diabetes mellitus; Vascular smooth muscle cell

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