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C-peptide prevention against diabetic complications

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C-peptide is a bioactive peptide with a potentially protective role in diabetes complications; however, its molecular mechanism of protection against vascular damage caused by hyperglycemia- or hyperglycemic memory-induced apoptosis remains unclear. We investigated the protective mechanism of C-peptide against hyperglycemia-induced vascular damage using human endothelial cells and streptozotocin-induced diabetic mice. C-peptide supplement therapy prevented activation of transglutaminase 2 and apoptosis in endothelial cells as well as in the aorta, heart, and kidney of diabetic mice. C-peptide activated AMP-activated protein kinase α and prevented intracellular ROS-mediated mitochondrial fission, mitochondrial membrane potential collapse, and endothelial cell apoptosis. C-peptide also ameliorated impaired wound healing by stimulating angiogenesis and inhibiting inflammation. Additionally, C-peptide prevented VEGF-induced microvascular permeability by inhibiting ROS-mediated activation of transglutaminase 2 in retinas of diabetic mice. Furthermore, we investigated the beneficial effect of C-peptide on hyperglycemic memory-induced vascular damage. Hyperglycemic memory induced apoptosis by persistent generation of intracellular ROS and sustained formation of $ONOO^-$ and nitrotyrosine. These hyperglycemic memory-induced intracellular events were normalized by C-peptide, but not by insulin, in endothelial cells and the aorta of diabetic mice. Thus, C-peptide prevents against hyperglycemia- or hyperglycemic memory-induced vasculopathy, suggesting that C-peptide replacement may be a promising therapeutic strategy to prevent diabetic complications.