

Abstract

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I-Carnitine attenuates angiotensin II-induced proliferation of cardiac fibroblasts: role of NADPH oxidase inhibition and decreased sphingosine-1-phosphate generation.

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BACKGROUND: The heart is unable to synthesize l-carnitine and is strictly dependent on the l-carnitine provided by the blood stream; however, additional studies are needed to better understand the mechanism of l-carnitine supplementation to the heart.

OBJECTIVE: The aim of this study was to evaluate the effects of l-carnitine on angiotensin II (Ang II)-induced cardiac fibroblast proliferation and to explore its intracellular mechanism(s).

METHODS: Cultured rat cardiac fibroblasts were pretreated with l-carnitine (1-30 mM) then stimulated with Ang II (100 nM).

RESULTS: Ang II increased fibroblast proliferation and endothelin-1 expression, which were partially inhibited by l-carnitine. l-Carnitine also attenuated Ang II-induced NADPH oxidase activity, reactive oxygen species formation, extracellular signal-regulated kinase phosphorylation, activator protein-1-mediated reporter activity and sphingosine-1-phosphate generation. In addition, l-carnitine increased prostacyclin (PGI(2)) generation in cardiac fibroblasts. siRNA transfection of PGI(2) synthase significantly reduced l-carnitine-induced PGI(2) and its anti-proliferation effects on cardiac fibroblasts. Furthermore, blockading potential PGI(2) receptors, including immunoprecipitation (IP) receptors and peroxisome proliferator-activated receptors alpha (PPARalpha) and delta, revealed that siRNA-mediated blockage of PPARalpha considerably reduced the anti-proliferation effect of l-carnitine.

CONCLUSIONS: In summary, these results suggest that l-carnitine attenuates Ang II-induced effects (including NADPH oxidase activation, sphingosine-1-phosphate generation and cell proliferation) in part through PGI(2) and PPARalpha-signaling pathways.

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