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اصول تنظیم قراردادها

آموزش مهارت های کاربردی در تدوین و چاپ مقاله
Short Term Administration of L-Carnitine can be Detrimental to the Ischemic Heart

Moslem Najafi*, Alireza Garjani

Department of Pharmacology, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

SUMMARY

Previous studies have shown that L-carnitine (LC) supplementation may exert a cardioprotective effect in cardiomyopathy, prevent arrhythmias in myocardial infarction and increase exercise tolerance in angina. Interestingly, we demonstrated that short term preischemic administration of LC can be detrimental to ischemic heart. In isolated rat hearts treated with LC for 10 min before ischemia, a marked and concentration dependent arrhythmogenic activity were produced during both ischemia and reperfusion as increases in the number of ventricular ectopic beats, ventricular tachycardia and incidence of ventricular fibrillation. We hypothesized that preischemic using of LC for an inadequate time may pose arrhythmogenic activity, due to incomplete metabolism of fatty acids which in turn lead to production of toxic long chain fatty acid metabolites and also because of interruption in glucose oxidation.

Introduction

Carnitine is an essential cofactor in the intermediary metabolism and in transport of long-chain fatty acids from the cytoplasm of cells to the mitochondrial matrix for ATP production under physiological conditions. This pathway within the mitochondria is the major source of energy for the heart. During myocardial ischemia, depressed oxygen supply results in carnitine release from the ischemic myocardium, and uncoupling of oxidative phosphorylation, leading to the accumulation of β-hydroxy fatty acid metabolic intermediates in the myocytes. In this condition, the fatty acids and their intermediates can be deleterious to the recovery of myocardial function of the reperfused heart. On the other hand, recovery after ischemia has been shown to be impaired by reducing the availability of fatty acid during reperfusion so that increase in fatty acid oxidation can be detrimental to cardiac recovery during reperfusion in ischemic tissues. Many previous experimental and clinical trials studies have shown that L-carnitine (LC) exerts a protective effect against ischemia/reperfusion (I/R) injuries in cardiomyopathies, reduction of infarct size and prevention of arrhythmias in patients with myocardial infarction (MI), increased exercise tolerance in angina and protection from the cardiotoxicity of the anthracycline antineoplastics. Cui et al. (2003) in an in vitro study investigated the effects of LC and propionyl LC on the incidence of reperfusion-induced VF (ventricular fibrillation) during global ischemia. Their results showed that different concentrations of LC failed to reduce the incidence of VF. However, incidence of reperfusion VF was significantly reduced in the hearts perfused with 5 mM propionyl LC only. Suzuki et al. reported that intravenous pretreatment of the ischemic dog heart by LC (100 mg/kg) reduced the grade of ventricular arrhythmias. They suggested that the administration of LC might be beneficial to prevent serious arrhythmias in ischemic heart disease, presumably by restoring the impaired free fatty acid oxidation. Some other experimental studies have shown that LC reduces myocardial injury after I/R by counteracting the toxic effect of high levels of free fatty acids, which occur in ischemia, and also by improving carbohydrate metabolism via reduction of intramitochondrial ratio of acetyl-CoA to free CoA, thus stimulating the activity of pyruvate dehydrogenase (PDH).

Hypothesis

It seems that protective effects of LC against I/R-induced cardiac arrhythmias can occur only by proper dose and enough treatment duration when the glycolysis is stimulated; so that we hypothesized that short term administration of LC may exhibit arrhythmogenic activity by promoting fatty acid metabolism.

Hypothesis evaluation

To evaluate the hypothesis, isolated hearts of male Sprague-Dawley rats (270-330 g) were rapidly...
mounted on a non-recirculating Langendorff apparatus under 100 mmHg pressure at 37.5 °C and perfused with modified Krebs–Henseleit (K/H) solution. A fluid filled balloon was introduced into the left ventricle and inflated to give a pre-load of 8–10 mmHg.7,9 Regional ischemia (30 min) induced by occlusion of left anterior descending coronary artery then by de-occluding of the coronary artery, the hearts allowed to be reperfused for 30 min.5 Based on the Lambeth conventions, the ECGs were analyzed to determine the total number of ventricular ectopic beats (VEBs), the number of beats occurring as ventricular tachycardia (VT), and the incidence and duration of VT and VF during 30 min ischemia followed by 30 min reperfusion.7 The isolated hearts were allocated randomly to one of following groups (n=10-12 in each group): (a) drug free control; (b) the hearts which were perfused with 0.5, 2.5 and 5 mM of LC-enriched K/H solution for the whole period of I/R (Protocol A); (c) or during 10 min before to 10 min after ischemia (Protocol B).

Findings
Perfusion of the agent for the whole period of I/R (Protocol A) produced significant (p<0.05) and concentration dependent reduction in the number of VT (max 65%) during reperfusion. The incidence of reperfusion VF was also decreased from its control value of 63% to 17% in the hearts perfused with 5 mM of LC, as reflected by a significant (p<0.05) decline of VF duration from 218±99 sec in control to 19±10 sec. However, preischemic administration of LC (Protocol B) by concentrations of 2.5 and 5 mM produced significant elevation in the total number of VEBs from 667±116 in the control to 1227±161 and 1289±171 in the treated groups, respectively. This increase was due to an increase in the number of VT. In this protocol, the incidence of VF was also elevated from 18% (control) to 67% in 5 mM LC treated hearts, as reflected by a significant raise in the total time spent in VF.

Discussion
The heart derives as much as 70 % of its energy needs from the catabolism of fatty acids.2 Anoxia caused by myocardial ischemia has been experimentally proven associated with the depletion of carnitine reserves and accumulation of toxic metabolites of fatty acid esterification, in consequence of restricted fatty-acids mitochondrial β-oxidation. The result is a decrease of ATP concentration in the heart. After only a few minutes of ischemia, free fatty acids, long-chain acyl-CoA esters and acylcarnitine are all increased several times above the control level.1 Yamada et al. have shown that long-chain acylcarnitines incorporate into cytosolic membrane compartments in ischemic tissue.10 These molecules are lipophylic and may readily damage membrane lipids and particularly, membrane bound enzymatic proteins,1 increase intracellular calcium ions, intracellular sodium ions and may thereby lead electrophysiologic and contractile dysfunction in the myocardium.13,14 In addition, accumulation of acylcarnitine esters in ischemic myocardium could contribute to the development of apoptosis.4 In fact, treatments to facilitate β-oxidation in the postischemic heart through the addition of carnitine have proven to be beneficial to myocardial recovery.2

Despite the important role of carnitine in the energy metabolism and fatty acid oxidation in the heart,2 we hypothesized that the role of concentration and duration of LC administration are critical factors for its antiarrhythmic or arrhythmogenic activity. Even the role of administration period is more important than the concentration of LC in this condition. The results of this study supported our hypothesis. Our results showed that perfusion of LC for the whole period of I/R (Protocol A) significantly produced antiarrhythmic effects. In this condition, increasing the concentration resulted in greater antiarrhythmic activity. In contrast to Protocol A, short term preischemic administration of LC, exhibited arrhythmogenic activity during both ischemic and reperfusion phases. The arrhythmogenesis of LC was increased parallel to the concentration with a linear mode, so that higher concentration (especially 5 mM) showed significant arrhythmogenic activity. We suggested that incomplete metabolism of LCFAs in mitochondria secondary to short term administration and/or using low concentrations of LC accumulates toxic fatty acid metabolites (such as long-chain acylcarnitines and acyl-CoA) in the myocytes. Accumulation of the noxious molecules in the myocardium is one of the most important potential mechanisms for arrhythmogenic activity of LC that can trigger arrhythmias. We also supposed that inadequate concentration or short term perfusion of LC may probably interrupt the agent ability to activate PDH activity, glucose oxidation, and removing lactate and free radicals from myocytes.

In conclusion, these results show that LC produced a protective effect against I/R-induced arrhythmias only when it is perfused for the whole period of the experiment. Therefore, it seems that for clinical situations, supplementations of LC for a long period will necessary to produce effective protection against cardiovascular diseases.

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Conflict of interest
The authors report no conflicts of interest.

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L-carnitine and ischemic heart

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