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Carvedilol Reduces Mitochondrial Damage Induced by Hypoxanthine/Xanthine Oxidase

Relevance to Hypoxia/Reoxygenation Injury

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Abstract

The cardioprotective properties of new pharmaceuticals such as carvedilol might be explained by enhanced mitochondrial protection. The aim of this work was to determine the role of carvedilol in the protection of heart mitochondria from oxidative damage induced by hypoxanthine/xanthine oxidase, a known source of oxidative stress in the vascular system. Carvedilol reduced oxidative-stress-induced mitochondrial injury, as seen by the delay in the loss of the mitochondrial transmembranar potential ($\Delta\Psi$), the decrease in mitochondrial swelling, and the increase in mitochondrial calcium uptake. Carvedilol improved the mitochondrial respiratory activity in state III and offered an overall protection in the respiratory control and in the P/O ratios in mitochondria under oxidative stress. The data indicated that carvedilol was able to partly protect heart mitochondria from oxidative stress-induced damage. Our results suggest that mitochondria can be important targets for some cardioprotective pharmaceuticals.

Key Words: Mitochondria; oxidative-stress model; xanthine/hypoxanthine; carvedilol; mitochondrial permeability transition pore.

Introduction

Adenosine triphosphate (ATP) synthesis and the maintenance of mitochondrial and cytosolic calcium homeostasis are two processes driven by the H^+ electrochemical gradient in heart mitochondria. Both processes are essential for myocardium performance. The high-energy requirements of the cardiac muscle are almost exclusively met by mitochondrial ATP production. A decrease in oxygen availability, as in myocardial ischemia, could jeopardize mitochondrial function. This happens in several heart dysfunctions that occur when the oxygen supply is not sufficient to balance the rate of mitochondrial substrate oxidation. The role of mitochondria in ischemic heart disease (for reviews, see refs. *1* and *2*) is very important for designing and studying novel cardiovascular drugs.

Hypoxia and reoxygenation are known to damage mitochondria in a process associated with the so-called oxygen paradox, when the sudden availability of

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