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Carvedilol Inhibits the Mitochondrial Permeability Transition by an Antioxidant Mechanism

Paulo J. Oliveira,* Telma Esteves, Anabela P. Rolo, Carlos M. Palmeira, and António J. M. Moreno

Center for Neurosciences and Cellular Biology of Coimbra, Department of Zoology, University of Coimbra, Coimbra, Portugal

Abstract

It was previously shown that carvedilol, a β-adrenergic receptor antagonist with antioxidant properties, was able to inhibit the mitochondrial permeability transition (MPT). In the present work, the hypothesis was that the negative impact of carvedilol on the MPT was specifically the result of its antioxidant effect. For the current investigation, we used three different MPT inducers. MPT-associated events were tested to study the protective effect of both carvedilol and cyclosporin-A, the known MPT inhibitor. Carvedilol inhibited mitochondrial swelling with calcium plus phosphate and with calcium plus *t*-butylhydroperoxide, but not with calcium plus carboxyatractyloside. Carvedilol inhibited the oxidation of thiol groups with calcium plus phosphate ($p < 0.01$) and with calcium plus *t*-butylhydroperoxide ($p < 0.05$), but not with calcium plus carboxyatractyloside—in opposition to the full protection afforded by cyclosporin-A when using calcium and carboxyatractyloside. Our results showed that carvedilol was effective only when the MPT was triggered by a primary oxidative process. This finding implies that the antioxidant properties of carvedilol are crucial for the observed effects and reinforces the advantageous use of carvedilol in cardiac pathologies associated with enhanced cellular oxidative stress.

Key Words: Carvedilol; transition pore; mitochondria; calcium; oxidative stress.

Introduction

The mitochondrial inner membrane permeability can increase owing to a calcium-dependent phenomenon known as the *mitochondrial permeability transition* (MPT), which is caused by the formation of pores of protein nature (mitochondrial permeability transition pores [MPTP]). Agents like phosphate, pro-oxidant systems like *t*-butylhydroperoxide or xanthine oxidase plus hypoxanthine, and thiol crosslinkers, such as phenylarsine oxide or carboxyatractyloside (a conformational inhibitor of the adenine nucleotide translocator [ANT]), are known to decrease the calcium threshold for MPT induction *(1)*. During cardiac ischemia and reperfusion, heart mitochondria suffer from increased oxidative injury and accumulation of calcium and phosphate *(2,3)*. MPT activation by oxidative stress and the protection afforded by antioxidants has already been demonstrated in several studies *(4–6)*. The role of the MPT on myocyte reperfusion injury is well established and was proposed to be determinant for the fate of the cardiac cell *(7,8)*.

*Author to whom all correspondence and reprint requests should be addressed: Paulo J. Oliveira, PhD, Centro de Neurociências e Biologia Celular de Coimbra, Departamento de Zoologia, Universidade de Coimbra, P–3004-517 Coimbra, Portugal. E-mail: pauloliv @ci.uc.pt

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