Trimetazidine and liver preservation against ischaemia-reperfusion injury

Ismail B. Mosbah[1], Hassen B. Abdennebi[2], Mohamed A. Zaouali[1], Susagna Padrissa-Altes[1], Carmen Peralta[3], Joan Roselló-Catafau[1]

[1]Experimental Hepatology Unit, Instituto de Investigaciones Biomédicas de Barcelona, CSIC-IDIBAPS, Barcelona, Spain
[2]Laboratoire de Physiologie Humaine, Faculté de Pharmacie, Monastir, Tunisia
[3]Institut d'Investigacions August Piy Sunyer, IDIBAPS, Barcelona, Spain

Submitted: 31 October 2007
Accepted: 13 November 2007

Arch Med Sci 2007; 3, 3A: S59-S61

Corresponding author:
Joan Roselló-Catafau,
Experimental Hepatology Unit
Instituto de Investigaciones
Biomédicas de Barcelona
Roselló 161, 08036-Barcelona,
Spain
Phone: +34 93 363 83 33
Fax: +34 93 363 83 01
E-mail: jrcbam@iibb.csic.es

Abstract

Trimetazidine is an anti-ischaemic drug used for angina pectoris treatment. Recently, it has been shown that trimetazidine protects against hepatic ischaemia reperfusion injury. Several hypotheses have been proposed to explain the exact hepatoprotective mechanisms but they still remain unclear. This review assesses the possible mechanisms responsible for the increase of the liver's tolerance against ischaemia-reperfusion injury with special emphasis on: (1) the prevention of oxidative stress and protection of mitochondrial function; (2) the generation of vasoactive mediators such as nitric oxide and endothelins; and finally (3) the preservation of liver energy metabolism.

Key words: ischaemia-reperfusion injury, liver, trimetazidine.

Introduction

Ischaemia-reperfusion injury is an inherent phenomenon that results following major liver surgery procedures such as hepatic resections and hepatic transplantation. Both clinical situations lead to the interruption of hepatic blood flow to the organ (ischaemia) followed by its subsequent restoration (reperfusion), thus originating severe damage known as ischaemia-reperfusion injury (IRI) [1, 2]. It is well known that IRI impacts directly on liver morbidity and mortality post surgery, especially when steatosis is present [3].

During ischaemia, cellular damage is induced as a consequence of cellular adenosine triphosphate (ATP) depletion and lactate accumulation, this being concomitant with derangements in calcium homeostasis [4]. After reperfusion, the ischaemic injury is aggravated by the generation of toxic reactive oxygen species (ROS) as a consequence of blood flow restoration. This is accompanied by the subsequent generation of inflammatory mediators and neutrophil accumulation which contribute to the progress of hepatic lesion [4]. Consequently, the prevention of liver vulnerability against ischaemia-reperfusion damage is determinant to preserve the organ function in experimental and clinical settings.

Trimetazidine or (1-2(2,3,4-trimeoxibenzyl)-piperazine) (TMZ) is a clinically effective anti-ischaemic drug that is currently used in some European

countries to treat angina pectoris [5, 6]. Its anti-ischaemic property is thought to be due to its ability to limit ATP depletion and intracellular acidosis [7]. Also, TMZ is able to reduce the generation of toxic free radicals during reperfusion [7]. Recently, there is increasing evidence that the cardioprotective effects exerted by TMZ can be extrapolated to the liver. This review assesses the possible protective mechanisms of TMZ against warm and cold liver ischaemia-reperfusion injury, especially in the presence of steatosis.

Protective mechanisms of TMZ against liver IRI

TMZ and its derivatives protect the liver against warm and cold ischaemia reperfusion injury [8-14]. These beneficial effects were initially associated with its antioxidant effects but the mechanisms responsible for this hepatoprotection seem to be more complex, and they include the involvement of freely diffusible molecules/radicals, such as nitric oxide (NO) and adenosine, which can act in autocrine and/or paracrine fashion as triggers to induce more protection and activate different transduction cell signalling factors, such as hypoxic inducible factor (HIF) [15].

Oxidative stress and mitochondrial function

Reactive oxygen species (ROS) production occurring during the ischaemia-reperfusion process seems to be a major determinant of tissue injury. These ROS are generated from both intracellular and extracellular sources [16] but liver mitochondria appears to be the most important [17]. TMZ reduced liver oxidative stress under warm ischaemia-reperfusion [8], this being well correlated with the preservation of mitochondrial function when TMZ was administered at the optimal dosage of 10 mg/kg/day [18]. Recent studies revealed that preservation of mitochondrial function exerted by TMZ in liver appears to be due to the closure of the mitochondrial permeability transition pore [10]. In line with this, we have recently demonstrated that TMZ addition to UW solution effectively preserved normal and steatotic livers against cold ischaemia-reperfusion injury [13, 14].

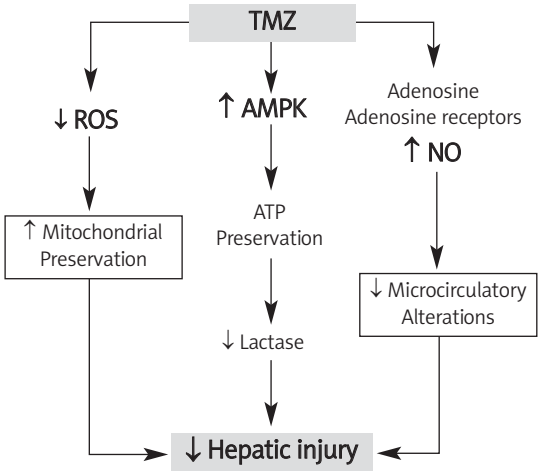

Figure 1. Proposed mechanisms responsible for hepatoprotection induced by TMZ against liver ischaemia-reperfusion injury

Nitric oxide

Nitric oxide (NO) is an important protective molecule due to its vasodilator and antioxidant properties. NO exerts its beneficial effects on oxidative stress in fatty livers undergoing ischaemia-reperfusion. Data showing the implication of NO in the cardioprotective effects of TMZ are scarce [19]. In this line, our recent investigations on fatty liver preservation point to the direct involvement of NO in the hepatoprotection induced by TMZ against ischaemia-reperfusion injury. We have demonstrated that this transient generation of NO was produced as a consequence of activation of the constitutive nitric oxide synthase (cNOS) when steatotic livers were preserved in UW solution enriched with TMZ [14]. Thus, the NO formed would contribute to ameliorating the oxygenation of hepatic tissue [20] and to preventing the altered microcirculation in fatty livers due to fat accumulation in liver sinusoids [21].

Additional NO benefits could also be associated with its inhibitory action on liver endothelins (ETs) [22]. Endothelins are potent vasoconstrictor peptides generated during earlier stages of liver reperfusion which are responsible for the reduction of sinusoid diameter with the subsequent induction of microcirculatory derangements, especially when steatosis is present [21]. These increased NO levels induced by TMZ could be associated with increases in adenosine release to the extracellular space as a consequence of the activation of specific adenosine receptors, as similarly occurred in liver ischaemic preconditioning [23] (Figure 1). In this sense, the increased adenosine plasma levels determined in treated TMZ patients affected by angina pectoris [24] seem to confirm this hypothesis. The administration of specific adenosine receptor antagonists in experimental models of warm ischaemia-reperfusion could clarify which kind of adenosine receptors are directly involved in the protective mechanisms induced by TMZ.

Energy metabolism

It is clear that TMZ improves energy recovery in different ischaemic models [9, 13, 14]. Recent studies carried out by our group evidenced that these beneficial effects are mediated by the activation of adenosine monophosphate protein kinase (AMPK) [14], a primary sensor of changes in cell energy during ischaemia. Fatty livers conserved in UW solution enriched with TMZ showed effective prevention of energy metabolism breakdown which correlated with

benefits in hepatic injury and liver function [14], respectively. In these conditions, the presence of AMPK inhibitors in UW solution abolished all the NO-dependent benefits of TMZ [14].

Signal transduction

Hypoxia-inducible factor (HIF) generated during hypoxic injury has recently been implicated in the regulation of mitochondrial signalling, hypoxic cell death and recovery from IRI [15]. Overexpression of HIF was induced in TMZ treated pig kidneys subjected to ischaemia-reperfusion [25]. These interesting results justify addressing further investigations to explore the potential role of HIF in the hepatoprotective mechanisms induced by TMZ against warm and cold ischaemia-reperfusion injury.

In conclusions TMZ protected the liver against warm and cold ischaemia-reperfusion injury and ameliorated liver function in steatotic and non-steatotic livers. Further investigations will be needed to elucidate the exact hepatoprotective mechanisms and evaluate whether TMZ treatments could be promising in major liver surgery procedures such as hepatectomies and orthotopic liver transplantation.

Acknowledgments

This work was supported by the Ministerio de Educación y Ciencia (project grant SAF 2005-00385), Ministerio de Sanidad y Consumo (project grant PIO60021) and Ministerio de Asuntos Exteriores y de Cooperación Internacional/Agencia Española De Cooperación Internacional.

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