A comparison of hepatic ischemia/hypoxia–reperfusion injury models

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Introduction: A number of hepatic ischemia/hypoxia–reperfusion models have been described. This study characterised the functional and structural changes induced by the most commonly used in vivo and in situ models for hypoxia/ischemia–reperfusion in the rat liver. Methods: A range of no-flow, slow-flow and lobular ischemia and reperfusion models were established in the rat liver. Changes following reperfusion were monitored using physiological, biochemical, histological and pharmacological assessments, including bile production, oxygen consumption, lactic acid extraction, enzyme release, and disposition of exogenous markers. Results: Short periods of hepatic ischemia/hypoxia–reperfusion led to minimal changes in liver function whereas long periods of ischemia–reperfusion led to substantial liver injury. The most severe injury was found with the slow-flow, reflow model. The formation of cell vacuoles, blebs and focal hepatic necrosis were the most important liver morphological changes observed as a consequence of ischemia/hypoxia. The major liver histological findings after reperfusion were dispersed apoptosis and local necrosis. Hepatic ischemia/hypoxia–reperfusion was also associated with significant changes in the hepatic extracellular and intracellular spaces. Discussion: The morphology and function of the liver associated with a range of hepatic ischemia/hypoxia–reperfusion models varies with the duration of the insult and between models. The choice of model is therefore an important consideration in seeking to resolve any particular hypothesis associated with hepatic ischemia/hypoxia–reperfusion.

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1. Introduction

Reperfusion/reoxygenation of a previously ischemic/hypoxic tissue or organ can lead to structural and functional alterations in that tissue or organ. Hepatic ischemic/hypoxic reperfusion injury may follow stroke, shock, cirrhosis, liver surgery and transplantation (Arab, Sasani, Raffee, Fatemi, & Javaheri, 2009; Bailey & Reinicke, 2000; Gao et al., 1992; Vizzotto, Vertemati, Degnà, & Aseni, 2001). A number of in vivo and in situ ischemia/hypoxia–reperfusion models have been used to characterise such injury in the liver and have been associated with differing pathophysiological changes that vary in the nature and extent between the various reported studies. The described experimental models differ in many aspects. For instance, the total stop-flow model involves ischemia of the whole isolated perfused liver (Jaeschke, Smith, & Mitchell, 1988a, 1988b) whereas in vivo lobar ischemia involves stopping blood flow to one or two lobes of the liver only (Hayashi, Chaudry, Clemens, & Raue, 1986). An alternative to stopping flow is to use a slow-flow–reflow liver perfusion model (Bradford, Marotto, Lemasters, & Thurman, 1986) or to perfuse the liver with a nitrogen-saturated buffer (Jaeschke & Mitchell, 1989). One advantage of using an in situ isolated perfused rat liver, as distinct from the in vivo liver, is the retention of its characteristics unaffected by what occurs in the rest of the body, a maintenance of hepatic structure and liver sinusoid oxygen gradients and an ability to characterise zonal-specific liver injury (Arab et al., 2007; Nishimura et al., 1986).

The present study sought to compare the nature and extent of hepatic injury induced by a range of in vivo and in situ ischemia/hypoxia–reperfusion models. Changes in perfusion pressure, bile production, oxygen consumption, wet:dry weight ratio, lactic acid extraction, enzyme release and multiple indicator dilution (exogenous solute) studies, histology (light and electron microscopy) and exogenous