Effect of Surgically Induced Cholestasis on the Levels of Hepatic Zinc and Metallothionein in Rat Liver

E. Brambila, *, 1 J. L. Munoz-Sanchez, 2 M. P. Waalkes, 3 and A. Albores 4

1Facultad de Ciencias Quimicas, Benemerita Universidad, Autonoma de Puebla, Mexico; 2Escuela Nacional de Ciencias Biologicas, Instituto Politecnico Nacional, Mexico City, Mexico; 3Inorganic Carcinogenesis Section, Laboratory of Comparative Carcinogenesis, National Cancer Institute at National Institute of Environmental Health Sciences, Research Triangle Park, NC 27706; and 4Departamento de Farmacologia y Toxicologia, Seccion de Toxicologia Ambiental, Centro de Investigacion y Estudios, Avanzados del IPN, Mexico

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ABSTRACT

Early effects of experimental cholestasis on the homeostasis of zinc (Zn) and metallothionein (MT) were studied in rats which had undergone bile duct ligation for 0, 3, 6, 9, 12, 16, 20, and 24 h. Transient increases in hepatic Zn levels were observed at 9 h but returned to control values at 12 h. Serum Zn levels increased at 24 h. Cholestasis was confirmed by increased serum alkaline phosphatase (AP) activity. MT increased at 3 h and reached a maximum level at 12 h and remained elevated even at 24 h after the onset of experimental cholestasis. No hepatocellular damage was detected according to the results of alanine aminotransferase (ALT) activities in serum. These results shown that the increases in Zn observed in liver are related to bile stagnation rather than to a hepatocellular damage and that increased MT occurs concurrently with increased hepatic Zn. These observations suggest that the cellular levels of Zn in

*Author to whom all correspondence and reprint requests should be addressed at: Inorganic Carcinogenesis Section, NCI at NIEHS, 111 Alexander Drive, Bldg. 101 SC MD:FO-09, RM F095, Research Triangle Park, NC, 27706.
cholestasis is regulated by homeostatic mechanisms, of which one could be mediated by MT.

Index Entries: Zinc; metallothionein; cholestasis.

INTRODUCTION

Cholestasis is caused by an obstruction of the bile duct, leading to the accumulation of bile that may alter the levels of zinc (Zn) in serum, liver, and urine. The effects of the bile obstruction on Zn metabolism are controversial because some studies find patients with extrahepatic cholestasis present low levels of Zn in blood and liver and increased urinary Zn (1,2); others have reported a decrease in blood Zn, but no alterations in urinary Zn (3). In addition, children of the Canadian native Ojibwa-Cree tribe suffering from severe cholestasis show increased hepatic Zn concentrations (4). It is unclear if the accumulation of Zn is a consequence of a genetic disorder, probably similar to that of Wilson’s disease for copper accumulation, or the result of an increase in dietary Zn, or from both. Although these authors suggest that the accumulation of Zn in the liver may cause the cholestasis (4), there is not enough experimental evidence to support this concept (5). Scheinberg and Sternlieb proposed that the increases in the content of Zn in these livers of the Canadian natives could be the result of an inherited flaw in the metabolic regulation of this metal.

Hepatic Zn homeostasis is at least partially regulated by metallothionein (MT), a low-molecular-weight cysteine-rich protein present in the cytosol of hepatocytes and many other cells (7). The synthesis of MT in the liver is largely under the control of the intracellular concentration of Zn (8,9), although many of the metals or nonmetallic agents can induce hepatic MT (10).

Nevertheless, it is clear that the levels of Zn in the liver are affected by long-term bile flow obstruction, the behavior of Zn and MT in the liver during the early stages of bile stagnation as in a cholestasis episode have not been well characterized. Therefore, the aim of this study was to investigate the changes in hepatic and serum Zn and hepatic MT levels resulting from experimental cholestasis.

MATERIAL AND METHODS

Animals and Treatments

Adult female Wistar rats (from the University of Puebla animal breeding facility) weighing 180–220 g were housed in polycarbonate animal cages with sawdust bedding and kept in controlled conditions (temperature, 23 ± 2°C; 12-h light cycle starting at 0600; 50% relative humidity); they were given food (Purina chow, Mexico) and water. However, food was withdrawn 12 h before experimental surgery.