purified astrocytes, and rats treated with MeHg (2, 4, 10 mg/kg for 3 days). MeHg exposure (0.1 to 100 μM) to cell-free brain homogenate produced dose-dependent decreases of GS activity. In mice given MeHg (2, 4, 10 mg/kg for 1 days), GS activity was inhibited in 4 or 10 mg/kg MeHg-treated groups. In cultured mixed glial cells, however, MeHg exposure (0-10 μM, for 6 days) resulted in dose-dependent increases of GS activity. In the mixed glial cells exposed to 5 μM MeHg only for 6 days, GS activity was significantly increased (2-fold), with no effects observed in MeHg-exposed cells for 6 to 48 hr. In primary cultures of mixed glial cells and astrocytes treated with MeHg (0, 5, and 10 μM), dose-dependent increases of GS activity were reconfirmed. GS activity was also significantly increased in frontal cortex and caudate nucleus of 4 or 10 mg/kg MeHg-treated rats for 3 consecutive days. To investigate the effect of glutamate on MeHg-induced GS activity, MeHg (10 μM) and glutamate (0.5 or 100 μM) were co-treated to the mixed glial cells and astrocytes for 6 days. Exposure of glutamate (0.5 or 100 μM) to mixed glial cells or astrocytes has no effect on GS activity. These data showed the differential effect of MeHg on GS activity in cell-free brain homogenate, cultured mixed glial cells, astrocytes, and MeHg-treated rodents, indicating that increases of GS activity are related to repeated (long-term) exposure to MeHg.

[OB-1] [10/18/2002 (Fri) 12:10 - 12:20 / Hall A]

Role of Kupffer Cells in Hepatic Drug Metabolizing Dysfunction during Polymicrobial Sepsis

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Although hepatocellular dysfunction occurs during sepsis, the mechanism responsible for this remains unclear. Since Kupffer cells provide signals that regulate hepatic response in endotoxin and inflammation, the aim of this study was to investigate the role of Kupffer cells in the alterations in the hepatic microsomal drug metabolizing function during sepsis. Rats were subjected to polymicrobial sepsis by cecal ligation and puncture (CLP) followed by fluid resuscitation. The gadolinium chloride ($GdCl_3$, 7.5 mg/kg), inactivator of Kupffer cells, was injected intravenously at 48 h and 24 h prior to surgery. Liver samples were taken 2 h and 6 h (early sepsis) and 24 h (late sepsis) after CLP for measurement of activities of cytochrome P-450 (CYP 450) isozymes and RT-PCR analysis of mRNA for CYP 450's genes. Activities of CYP 1A1, 1A2 and 2B1 in liver microsomal fraction were measured as 7-ethoxyresorufin O-deethylase, methoxyresorufin O-demethylase, and pentoxyresorufin O-dealkylase activities, respectively. Aniline p-hydroxylase activity (CYP 2E1) was determined by measuring the formation of p-aminophenol. Serum alanine aminotransferase activity in all experimental groups was unchanged. However, in CLP rats, serum aspartate aminotransferase activity and lipid peroxidation levels were significantly elevated after 24 h of CLP and the increase in lipid peroxidation was suppressed by $GdCl_3$ treatment. Total CYP 450 content was significantly decreased after 24 h of CLP but $GdCl_3$ had little effect on total CYP 450 content. NADPH-CYP 450 reductase activity reduced after 6 h of CLP and again after 24 h of CLP. $GdCl_3$ prevented the decrease in NADPH-CYP 450 reductase activity after 24 h of CLP. CYP 2B1 activity in all experimental groups was unchanged. CYP 1A1 and CYP 2E1 activities were both significantly decreased 24 h after CLP, which were prevented by $GdCl_3$ treatment. CYP 1A2 activity was decreased 2 h and 24 h after CLP. $GdCl_3$ restored CYP 1A2 activity to the level of sham-operated rats. mRNA level for tumor necrosis factor-α (TNF-α) in CLP rats was significantly increased throughout the experiment.$GdCl_3$ prevented the increase in TNF-α mRNA 24 h after CLP. In contrast, mRNA levels for NADPH-CYP 450 reductase, CYP 1A2 and CYP 2E1 were significantly decreased 24 h after CLP, which were prevented by $GdCl_3$. We conclude that both the decreased activity of CYP 450 isozymes and the down-regulation of CYP 450's genes occur during the late stage of sepsis. Kupffer cells may be responsible for producing hepatocellular dysfunction during sepsis.

[OC-1] [10/18/2002 (Fri) 16:00 - 16:10 / Hall B]