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Sepsis remains the leading cause of morbidity and mortality following trauma. Although hepatocellular dysfunction occurs during trauma and sepsis, the mechanism responsible for this remains unclear. We investigated the role of Kupffer cells in the alterations in microsomal drug metabolizing function during trauma and sepsis. Rats were subjected to trauma by femur fracture (FFx). After 72 h, polymicrobial sepsis was induced by cecal ligation and puncture (CLP). To inactivate Kupffer cells, the gadolinium chloride (GdCl₃, 7.5 mg/kg) was injected intravenously at 1 and 2 days prior to surgery. Liver samples were taken 2 h and 6 h (early sepsis) and 24 h (late sepsis). After CLP alone, serum AST activity and lipid peroxidation level were elevated 24 h after CLP and started to increase 2 h and remained constant upto 24 h after CLP in FFx + CLP, which were suppressed by GdCl₃. Total cytochrome P-450 (CYP 450) content was decreased in CLP alone. This decrease was potentiated after FFx + CLP. NADPH-CYP 450 reductase activity was reduced 6 h and again after 24 h of CLP in both CLP and FFx + CLP, which were prevented by GdCl₃ treatment. CYP 2B1 activity was decreased 2 h in FFx + CLP and GdCl₃ restored this decrease. CYP 1A1 activity was decreased 24 h in CLP alone and 6 h and 24 h after CLP in FFx + CLP. CYP 2E1 activity was decreased 24 h in CLP alone and remained depressed throughout the experiment in FFx + CLP, which were prevented by GdCl₃. CYP 1A2 activity was decreased 24 h in CLP alone and 6 h after CLP in FFx + CLP. We concluded that sepsis alone decreases the activity of CYP 450 isozymes during late stage of sepsis, while sequential injury potentiates this decrease during early and late sepsis. Activation of Kupffer cells may contribute to hepatocellular dysfunction.

Poster Presentations – Field B3. Neuroscience

[PB3-1] [10/17/2002 (Thr) 13:30 – 16:30 / Hall C]

Adenosine inhibits the death in immunostimulated murine astrocytes deprived of glucose

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Adenosine has been associated with protection of neurons from noxious stimuli both by receptor- and non receptor-mediated mechanisms. Previously we have reported that immunostimulated astrocytes were highly vulnerable to glucose deprivation. In the present study we investigated the effect of adenosine and related nucleotides on the susceptibility of immunostimulated astrocytes to glucose deprivation. While neither 12-h glucose deprivation nor 2-day treatment with IFN- γ and LPS altered the viability of astrocytes, significant death of IFN- γ /LPS-treated astrocytes was observed after 4-h glucose deprivation. The augmented astrocyte death was blocked by adenosine with an apparent EC50 value of 20 μ M. However, adenosine receptor agonist R-PIA or CHA did not inhibit the augmented cell death. Moreover, adenosine receptor antagonists DPCPX, XAC or DMPX did not alter the augmented death, ruling out the involvement of adenosine receptor in this process. Other purine nucleotides including guanosine, inosine, AMP, ADP and ATP, but not pyrimidine nucleotides such as cytosine, showed similar protective effects. Intracellular ATP level rapidly decreased prior to the release of LDH in immunostimulated astrocytes deprived of glucose. Adenosine and other purine nucleotides inhibited the loss of intracellular ATP. Since high micromolar concentrations of ATP and adenosine nucleotides were released in cerebral hypoxic/ischemic regions, ATP, adenosine and their metabolites may protect the astrocyte death by restoring intracellular ATP level, at least in our experimental systems.

[PB3-2] [10/17/2002 (Thr) 13:30 – 16:30 / Hall C]

Neuroprotective effects of baicalein, baicalin, and wogonin in primary cultured rat cortical cells