Title : SUPERIORITY OF REDUCED GLUTATHIONE TO METHYLPREDNISOLONE IN THE TREATMENT OF ENDOTOXIN SHOCK

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Introduction: Many investigators have reported that pharmacological doses of glucocorticoid have beneficial effects on several types of shock in experimental animals. Based on these studies, large doses of glucocorticoid are widely used clinically in treatment of shock. On the other hand, the tissue SH-compound (reduced glutathione or GSH) has been shown to decrease in traumatic, cardiogenic and endotoxin shock and in a number of other stressful situations. And recently exgenous GSH has been reported to increase the tissue GSH level and to have several beneficial effects on shock. However, studies compairing the effects of glucocorticoid and GSH on experimental shock have not been reported. The purpose of this study was to investigate the effects of glucocorticoid and GSH on survival rate and hepatic energy metabolism in endotoxin treated animals.

Methods:
SURVIVAL RATE; Dd strain mice of weighing about 30 g were used in this experiment. Mice were divided into nine groups. Each mouse was administered 50 mg/kg of endotoxin (Difco E. Coli endotoxin 0127 B 8) intraperitoneally. Groups of mice were injected either saline, GSH 200 mg/kg, GSH 500 mg/kg, Methylprednisolone (M-P) 10 mg/kg, M-P 30 mg/kg, GSH 200 mg/kg + M-P 10 mg/kg, GSH 200 mg/kg + M-P 30 mg/kg, GSH 500 mg/kg + M-P 10 mg/kg or GSH 500 mg/kg + M-P 30 mg/kg intraperitoneally 5 min. after endotoxin administration. The mortarity rates at 24 hrs. and 48 hrs. after endotoxin injection were determined.

HEPATIC ENERGY METABOLISM; Wister strain rats of weighing about 250 g were divided into four groups, control, saline-treated, GSH-treated and M-P-treated groups. All rats except in the control group were injected 50 mg/kg of endotoxin intraperitoneally. And then 5 min. after endotoxin injection, either saline, 500 mg/kg of GSH or 30 mg/kg of M-P was administered intraperitoneally. Five hrs. after endotoxin injection, rats were anesthetized with ether, and the livers were excised via midline incision and instantanuously placed in liquid nitrogen. Liver tissue was powdered in liquid nitrogen and weighed. Hepatic ATP, ADP and AMP were analyzed by the enzymatical method. Hepatic total adenine nucleotide (TAN) and energy charge (EC) were calculated by the next formula, TAN = ATP + ADP + AMP, EC = (ATP + 1/2 ADP)/(ATP + ADP + AMP).

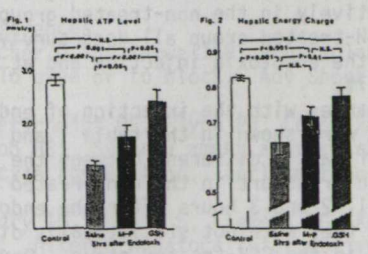
Results:
SURVIVAL RATE; The mortarity rates at 24 hrs. and 48 hrs. after endotoxin injection were shown in Table 1. The mortarity rate of the GSH group decreased proportionally with the dose of GSH. The mortarity rates in the GSH-treated group (500 mg/kg) were 47% at 24 hrs. and 71% at 48 hrs. after endotoxin injection. These were significantly lower than that of the saline-treated group. On the other hand, M-P administration did not show any beneficial effect, and the treatment with 10 mg/kg of M-P even demonstrated a tendency to increase the mortarity rate. The combined mortarity rate of four groups treated with both GSH and M-P was not different from that of the saline-treated group.

Table 1 Mortarity Rates

Methylprednisolone		Glutathione 0 mg/Kg	Glutathione 200 mg/Kg	Glutathione 500 mg/Kg
0 mg/Kg	24 hrs.	75% (39/52)	59% (10/17)	48% (8/17)*
	48 hrs.	100% (52/52)	88% (15/17)	71% (12/17)**
10 mg/Kg	24 hrs.	93% (14/15)	65% (11/17)	82% (14/17)
	48 hrs.	100% (15/15)	88% (15/17)	100% (17/17)
30 mg/Kg	24 hrs.	80% (12/15)	56% (9/16)	65% (11/17)
	48 hrs.	87% (13/15)*	93% (15/16)	94% (16/17)

$P<0.05$ (*), $P<0.01$ (**) from non-treatment group

HEPATIC ENERGY METABOLISM; The hepatic ATPs in four experimental groups were shown in Fig. 1. The hepatic ATP in the control group was 2.82 μmol/g. In the saline-treated group, ATP was 1.22 μmol/g, and was significantly lower than those in the other three experimental groups. The ATP in the M-P-treated group was higher than that in the saline group, however, it was lower than those in the control and GSH-treated group. On the other hand, the ATP in the GSH-treated group was not different from the control. The hepatic ADPs and AMPs in the three endotoxin injected groups were not different from each other. The TANs in the saline- and M-P-treated groups were lower than the control value. In GSH-treated group, TAN was not different from the control value. The Hepatic ECs were shown in Fig. 2. The ECs in the saline- and M-P-treated groups were lower than the value in the control group. The EC in the GSH-treated group was not significantly different from the control value.



Conclusion: The treatment with GSH decreased the mortarity rate and enhanced the hepatic energy metabolism in the endotoxin treated animals. However, the M-P treatment could not reduce the mortarity rate and showed less ability to enhance the hepatic energy metabolism than the GSH treatment in this experiment. These results suggest rationale to use GSH for clinical shock.