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EFFECT OF CYCLOSPORIN ON HEPATIC REGENERATION

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The Capacity of the liver to regenerate after orthotopic liver transplantation is a critical process that is dependent on numerous factors. The effect of drugs, especially immunosuppressive agents, administered during the period when the transplanted liver is most vulnerable is clearly important. We describe preliminary studies examining the effect of cyclosporine A (CsA) on hepatic regeneration when administered before or after 70% partial hepatectomy (PH) in rats.

MATERIALS AND METHODS

Male Fischer strain rats (F344) weighing 200 to 250 g were used in all studies. They received standard rat chow and water ad lib and were allowed to acclimatize for one week prior to experimentation. Standard 70% PH (1) was carried out between 9:00 A.M. and 12:00 P.M. Rats were randomly assigned to one of four groups (18 rats per group): In group I, sham PH followed ten minutes later by an intravenous (IV) bolus of CsA (5 mg/kg) (Sandoz Pharmaceuticals, NJ); in group II, PH followed ten minutes later by IV CsA vehicle; in group III, PH followed ten minutes later by an IV bolus of CsA (5 mg/kg); and in group IV, CsA administered orally in olive oil (25 mg/kg/d) for seven days prior to PH followed by an IV bolus of CsA (5 mg/kg) at ten minutes after PH.

Rats were killed every six hours for 48 hours after PH. Hepatic thymidine kinase (TK) and ornithine decarboxylase (ODC) activities, measured as previously described (2,3), were used as indices of hepatic regeneration. Blood CsA levels were assayed by high-performance liquid chromatography (4). All results are presented as a mean ± SE and compared using analysis of variance followed by Tukey's test ($P < 0.05$ was considered statistically significant).

RESULTS AND CONCLUSIONS

Table I presents the effect of CsA on those indices of hepatic regeneration measured in this study. CsA at the dosage used did not adversely affect any of these parameters. Acute CsA administration after PH (group III) had no effect on the induction of TK or ODC activity, while CsA pretreatment (group IV) potentiated the elevation of these two enzyme activities. Peak ODC activity, the rate-limiting factor in polyamine synthesis, was twofold higher in group IV rats than in controls (group II, $P < 0.05$). The effect of CsA on DNA synthesis was assessed by measuring TK activity, an enzyme whose activity has been correlated with mitotic index (2). There was a lesser effect of CsA on TK activity; CsA pretreatment resulted in a significant increase in activity only at 36 hours after PH (group IV, $P < 0.05$).

CsA pretreatment resulted in a significant reduction in liver cytosolic protein at 18 hours (data not shown) and 36 hours after PH compared to vehicle-treated controls (group IV vs. group II, $P < 0.05$). The cause of the lower cytosolic protein level is uncertain, since CsA

resulted in increased ODC activity and therefore increased protein synthesis in group IV rats. The weight of the liver remnant was significantly reduced in group IV rats at 36 hours after PH compared to group II (control) rats ($P < 0.05$).

Since results from subsequent experiments demonstrated that the olive oil vehicle used for oral administration of CsA had caused a slight weight loss in group IV rats, we concluded that CsA treatment in these experiments did not affect liver weight. As was expected based on hepatic clearance of CsA, PH decreased the rate of CsA disappearance, as indicated by an increase in the blood half-life of the drug. CsA pretreatment further decreased the disappearance rate, probably by saturating deposition sites.

The data presented in this study demonstrate that CsA in the dosages studied did not inhibit two enzymologic parameters of hepatic regeneration. Moreover, CsA pretreatment potentiated these indices. The importance of this finding remains to be determined. Although further dosages and schedules of CsA administration need to be studied, the lack of a deleterious effect on liver regeneration demonstrated in this study has significant implications for liver transplantation.

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Table 1

Effect of CsA on parameters of hepatic regeneration

Group*	*n*	Peak ODC (cpm/mg/h)	36-h TK (fmol/mg/min)	36-h Cytosolic protein (mg/mL homogenate)	Liver weight (g)	CsA half-life (h)
I	3	86 ± 3†	256 ± 110†	20.0 ± 1.2	ND	9
II	3	399 ± 50	1387 ± 95	22.4 ± 1.8	5.23 ± 0.15	…
III	4	379 ± 43	1202 ± 137	19.3 ± 1.2	5.05 ± 0.33	15
IV	3	928 ± 161†	2020 ± 140†	14.4 ± 0.4†	4.20 ± 0.11†	82
Untreated	6	38 ± 5	319 ± 25	17.6 ± 0.9	ND	…

*Groups: I = sham partial hepatectomy follwed by CsA bolus, II = partial hepatectomy followed by CsA vehicle only, III = partial hepatectomy followed by CsA bolus, IV = CsA pretreatment and then partial hepatectomy followed by CsA bolus.

†$P < 0.05$ vs. group II.