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Cyclosporine A Augments the Regenerative Response After Partial Hepatectomy in the Rat

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Injury to the liver results in a regenerative response that is characterized by proliferation of both parenchymal and littoral cells. During orthotopic transplantation of the liver, the liver may be injured by ischemia during the harvesting procedure and by rejection in the posttransplant period. Cyclosporine A (CsA), a powerful immunosuppressive agent, is used routinely after orthotopic liver transplantation, and it thus seemed appropriate and important to study the effect of CsA on hepatic regeneration.

MATERIALS AND METHODS

Male Wistar rats weighing 250 to 300 g were randomly assigned to three groups and treated as follows:

Group I

Days 1–7, CsA in olive oil 25 mg/kg orally; day 8, CsA in saline 5 mg/kg intravenously (IV) followed by partial hepatectomy (PH).

Group II

Days 1–7, olive oil vehicle orally; day 8, saline IV followed by PH.

Group III

Days 1–7, CsA in olive oil 25 mg/kg orally; day 8, CsA in saline 5 mg/kg IV followed by sham PH.

Standard 70% PH[1] and sham PH were carried out between 8:00 AM and 11.00 AM to avoid the effect of diurnal variation. All surgical procedures were performed under ether anesthesia.

Rats were killed at 6, 24, and 48 hours after partial hepatectomy. The remnant livers were removed and weighed, and used to measure hepatic thymidine kinase (TK) and ornithine decarboxylase (ODC) activities, as described previously.[2,3] All results are presented as a mean ± SEM and compared using analysis of variance.

RESULTS

The liver weight/body weight (LW/BW) ratio, shown in Table 1, remained unchanged after sham PH. However, there was a steady increase in LW/BW ratio after PH and by 72 hours was almost the same as control values. The LW/BW ratios were similar after PH in rats pretreated with CsA and those pretreated with the vehicle.

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Preoperative ODC activity (Table 2) was significantly higher in rats pretreated with CsA (P <. 01). At six hours, levels of ODC activity were significantly elevated in all three groups ($P < .01$), with the levels of activity being highest in rats treated with CsA and PH. The ODC activity returned to normal at 24 hours in rats subjected to sham PH, but was still significantly elevated after PH; again, levels were highest in rats treated with CsA and PH.

The changes in TK activity are shown in Table 3. Preoperative levels of TK activity were also significantly higher in rats pre-treated with CsA ($P < .01$). Levels of TK activity were not elevated at 24 hours after sham PH and were in fact lower than preoperative values. There was a significant increase in TK activity at 24 hours after PH, with levels being significantly higher in rats pre-treated with CsA ($P < .05$).

Preoperative liver function tests in rats pre-treated with CsA were similar to those pre-treated with the vehicle (Table 4). There was a significant increase in SGOT levels associated with the injury of the PH, and also a small but significant increase after sham PH. The injury pattern after PH was less in rats pretreated with CsA.

DISCUSSION

The capacity of the liver to regenerate in response to various forms of injury has been studied extensively. In recent years transplantation of the liver has become accepted as a viable alternative in the management of patients with end-stage liver disease. During liver transplantation the liver may be injured in a number of ways, including the ischemic injury during harvesting and the immunologic attack by the host. Certain drugs used in the posttransplant period may also be toxic to the liver. CsA is used routinely in the immunosuppresive regimen after liver transplantation and its side-effects include hepatotoxicity. It thus seemed important to study the effect of CsA on hepatic regeneration.

The effect of CsA on the regenerative response may also be relevant in certain cases of pediatric liver transplantation where, because of the critical shortage of suitable pediatric donors, many centers have resorted to using reduced-size adult liver grafts. A normal regenerative response may be necessary for the successful outcome of these grafts.

ODC is the rate-limiting enzyme in poly-amine synthesis, and increased polyamine synthesis is thought to play a critical role in the stimulation of hepatic regeneration after partial hepatectomy. In addition, regeneration of the liver involves an increase in DNA synthesis in the liver, which requires an induction of hepatic TK activity. Thus, these two enzymes were used as indices of liver regeneration. Both TK activity and ODC activity were significantly higher after partial hepatectomy in rats pretreated with CsA.

Thus, there appears to be increased hepatic regeneration after partial hepatectomy in rats treated with CsA. CsA is known to be hepatotoxic and this may account for the greater regenerative response. However, preoperative liver function tests in the rats pretreated with CsA were the same as control values. On the other hand, the injury may be subclinical and not detected by routine tests of liver function.

It may be that CsA induces both ODC and TK. This would account for the significantly higher preoperative levels of activity of both enzymes in rats pretreated with CsA and would explain the significant elevation in ODC at six hours after sham operation.

The data presented in this study demonstrate that CsA at the dosage used did not adversely affect hepatic regeneration after partial hepatectomy in rats and actually resulted in a greater regenerative response.

Acknowledgments

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References

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Table 1

Liver Weight/Body Weight Ratios ($\times 10^3$) in Rats Treated With CsA and PH (Group I), Vehicle and PH (Group II), and CsA and Sham PH (Group III) (Mean ± SEM)

	Group I	Group II	Group III
6 h	97 ± 6	105 ± 5	262 ± 10
24 h	117 ± 4	146 ± 14	269 ± 4
48 h	168 ± 9	147 ± 21	252 ± 5

Table 2

ODC Activity (cpm/mg Protein) in Rats Treated With CsA and PH (Group I), Vehicle and PH (Group II), and CsA and Sham PH (Group III) (Mean ± SEM)

	Group I	Group II	Group III
Preoperative	726 ± 18	546 ± 11	726 ± 18
6 h	4,984 ± 337	3,096 ± 785	2,573 ± 238
24 h	3,619 ± 631	2,068 ± 711	685 ± 18
48 h	2,319 ± 242	2,557 ± 128	741 ± 28

Table 3

TK Activity (dpm/mg Protein) in Rats Treated With CsA and PH (Group I), Vehicle and PH (Group II), and CsA and Sham PH (Group III) (Mean ± SEM)

	Group I	Group II	Group III
Preoperative	4,364 ± 847	1,246 ± 219	4,364 ± 847
6 h	4,403 ± 1,242	581 ± 90	1,525 ± 101
24 h	16,777 ± 581	11,110 ± 1,269	1,098 ± 76
48 h	10,736 ± 640	12,623 ± 1,457	3,921 ± 749

Table 4

Serum SGOT levels (Mean ± SEM) in Rats Treated With CsA and PH (Group I), Vehicle and PH (Group II), and CsA and Sham PH (Group III)

	Group I	Group II	Group III
Preoperative	83 ± 18	85 ± 8	83 ± 18
6 h	1,520 ± 407	1,146 ± 167	147 ± 15
24 h	1,399 ± 78	2,467 ± 663	110 ± 2
48 h	543 ± 100	1,976 ± 800	106 ± 8