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Protective Effect of TNF-*α* and IL-1*β* Inhibitor FR167653 on Ischemia-Reperfusion Injury in Rat Small Intestinal Transplantation

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RECENTLY, it has been demonstrated that the proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-1 may play an important role in ischemia-reperfusion (I-R) injury in several organs such as the liver, lung, kidney, heart, and small intestine, both in nontransplant and in transplant experimental models,1›2 as well as in clinical transplant cases.3 A newly developed agent, FR167653 (FR), has recently been shown to have potent specific inhibitory effects on TNF-*α* and IL-1*β* activity in vitro and in vivo. In this study, we investigated the protective effect of FR on I-R injury of intestinal grafts as well as remote organs such as liver, kidney, and lung in a rat transplantation model.

MATERIALS AND METHODS

Syngeneic orthotopic small intestinal transplantation (SIT) was performed using Lewis rats, in which the graft was preserved for 12 hours in cold (4°C) lactated Ringer's solution. FR was administered to the recipients intravenously for 4 hours starting at 30 minutes prior to reperfusion, at the dose of 0.25 mg/kg per hour (FR group), or vehicle (saline) only (control group). Animal survival, histology of small intestinal graft, plasma levels of TNF-*α* and IL-1*β*, plasma GPT and creatinine, tissue myeloperoxidase (MPO) activity, as well as neutrophil infiltration in lung, were compared.

RESULTS

Eleven of 14 animals in the FR group survived over 48 hours after transplantation, whereas only 5 animals survived in the control group ($P < .05$). There was no difference in the grading score of intestinal graft injury between the groups. Plasma level of TNF-*α* in the FR group was significantly suppressed at 12 hours after reperfusion compared to the control group (56.6 ± 39.6 versus 101.8 ± 34.2 pg/mL), whereas that of IL-1*β* was significantly suppressed at 1 hour after reperfusion in the FR group compared to the control group (12.2 ± 5.9 versus 18.9 ± 15.0 pg/mL, $P < .05$). There was no difference in plasma GPT levels between the groups, whereas plasma creatinine level in the FR group was significantly improved at 4 and 12 hours after reperfusion compared to the control group (1.00 ± 0.09 versus 1.13 ± 0.08 mg/dL at 4 hours, $P < .05$; 0.88 ± .31 versus 1.45 ± 0.51 mg/dL at 12 hours, $P < .01$, respectively). Tissue MPO activity in the lung at 12 hours after reperfusion was significantly suppressed in the FR group compared to the control group (0.31 ± 0.08 versus 0.41 ± 0.10 ΔOD_{460}/min per g, $P < .05$), whereas neutrophil infiltration in the lung at 12 hours after reperfusion was significantly lower

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in the FR group compared to the control group (37.2 ± 7.7 versus 46.6 ± 8.3 in 10 HPF, $P < .05$).

CONCLUSION

In rat small intestinal transplantation, not the graft itself but the remote organs such as lung and kidney are the critical organs for ischemia-reperfusion injury. TNF-α and IL-1β are thought to be important mediators of ischemia-reperfusion related remote organ injury in lung and kidney. FR167653 is an effective drug to prevent the ischemia-reperfusion-related remote organ injury in rat small intestinal transplantation.

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