2142

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Loss of Serum Bicarbonate After Discordant Liver Xenotransplantation

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IT IS A concern in liver xenotransplantation (XTx) that discordant combinations might not be sufficiently compatible for physiologic functioning in the recipient. Closer examination of the guinea pig- (GP) to-rat liver XTx model uncovered potential incompatibilities in bile production between these species. GP (along with rabbits) have the greatest bile flow rate of all species studied.[1] Additionally, there is a fundamental difference between the two species in the rate of bile excretion. Bile flow in rats is bile acid dependent, whereas the rate in GP is independent of bile acid; the latter is believed to be driven osmotically by bicarbonate.[2] Because bile flow is 4 times greater in GP than in rats, we tested whether the different excretion mechanisms would affect HCO_3^- blood levels and pH in rat recipients of GP liver xenografts (Xeno).

MATERIALS AND METHODS

Hartley GP and LEW rats were used as donors and recipients, respectively. Orthotopic liver transplantation was performed as described by Miki et al.[3] Both syngeneic (LEW to LEW) liver graft recipients (Syn) and xenorecipients (GP to LEW) received cobra venom factor 80 U/kg on day −1 as well as 1 mg/kg im tacrolimus and 10 mg/kg mycophenolate mofetil daily by gavage for the duration of the experiment. Bile was collected in naive rats, naive GP, and liver-transplanted rats 15 minutes after the surgical procedure. Bile flow was measured every 15 minutes for an hour. Arterial blood samples were collected at 6 hours posttransplantation (post-Tx) and on days 1 and 2 to test blood gas values and bicarbonate using a gasometer.

RESULTS

Immunosuppression prolonged survival of xenorecipients from 3.1 ± 1.7 hours in untreated controls to a mean of 80.4 ± 9.8 hours. For the first two post-Tx days, these xenorecipients were active, behaved normally, and showed no histologic evidence of rejection or drug toxicity. As shown in Table 1, Syn recipients had normal blood gas values at all points measured post-Tx. However, in xenorecipients the HCO_3^- levels decreased dramatically as early as 6 hours post-Tx, with a subsequent fall in systemic pH levels. Levels of pco_2 also decreased as a result of respiratory compensation. Bile HCO_3^- levels in naive rats were 37.1 ± 2.7 mmol/L, but the HCO_3^- in GP bile was 3 times higher (103.8 ± 5.0 mmol/L). The GP phenotype was conserved post-Tx, where HCO_3^- levels reached 100 mmol/L on days 1 and 2.

Table 1. Blood Gas Analysis After Syngeneic and Xenogeneic Liver Transplantation

	pH	pco_2	HCO_3^-
Rat	7.38 ± 0.04	47.0 ± 4.9	27.9 ± 0.8
GP	7.40 ± 0.02	52.5 ± 5.4	26.5 ± 2.4
Syn 6 h	7.33 ± 0.02	49.4 ± 5.2	23.7 ± 1.1
Syn 24 h	7.40 ± 0.04	53.1 ± 1.9	26.5 ± 2.3
Syn 48 h	7.33 ± 0.05	55.5 ± 4.7	27.8 ± 0.3
Xeno 6 h	7.27 ± 0.04	41.1 ± 3.8	18.0 ± 0.8*
Xeno 24 h	7.24 ± 0.06*	37.5 ± 5.9*	17.2 ± 3.2*
Xeno 48 h	7.18 ± 0.06*	39.9 ± 5.8	16.1 ± 1.2*

*$P < .01$ versus all groups.

DISCUSSION

The higher concentration of HCO_3^- in the bile of GP livers together with the 4 times greater bile flow than rat led to a loss of HCO_3^- buffer and a tendency toward metabolic acidosis in xenorecipients. Similar problems may also occur after pig-to-human liver transplantation where the unstimulated biliary HCO_3^- concentration in pigs is 103 mEq/L[4] and that of humans is only 25 mEq/L. Immunologic discordancy may be accompanied by severe physiologic and metabolic incompatibilities, which must also be taken into consideration for multifunctional organs like the liver.

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0041-1345/00/$–see front matter
PII S0041-1345(00)01148-9