THE EFFECT OF INTERLEUKIN 1α ON ACETAMINOPHEN-INDUCED HEPATOTOXICITY

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The protective effect of interleukin 1α (IL-1α) in mice with acetaminophen (AAP)-induced hepatitis was investigated. IL-1α had a significant protective effect if given 2 or more hours (up to 24 hours) before AAP; it significantly reduced mortality of mice and decreased serum transaminase level. The maximal effect was obtained with the dose of 1000 U (166 ng/kg) IL-1α. Pretreatment with IL-1 significantly increased the synthesis of prostaglandin E_2 (PGE_2) in samples of liver tissue from AAP-treated mice, but had no effect on the synthesis of leukotriene C_4 (LTC_4). Pretreatment with indomethacin (IMC) did not abrogate significantly the protective effect of IL-1. Thus, the hepatoprotective effect of IL-1α can not be entirely explained by the stimulation of prostaglandin (PG) synthesis.

It is now well established that interleukin 1 (IL-1), especially IL-1α, has a cytoprotective effect on certain target tissues. Thus, it was shown that IL-1 protects hematopoietic cells from radiation-[1] or drug-induced[2] toxicity, as well as gastric epithelial cells against ethanol-induced damage.[3,4] Also, IL-1 protects against galactosamine/lipopolysaccharide (LPS) or galactosamine tumour necrosis factor (TNF) toxicity[5] and prevents lymphoid cell death by apoptosis in tissue culture.[6] The mechanism of this cytoprotective effect is still unknown. Some data indicate that the protective effect of IL-1 was mediated by prostaglandins. Thus, IL-1 is a potent inducer of PG synthesis (especially PGE_2) by various cells,[7–9] and second, PGE_2 and prostaglandin I_2 (PGI_2) have a potent cytoprotective effect. The cytoprotective effect of PGE_2 was demonstrated for radiation-induced damage of intestinal epithelium,[10] tumor cells[11] and chemically or immunologically induced damage of hepatocytes[12–14] and gastric epithelial cells.[15] Also, it was reported that protective effect of IL-1 in ethanol-induced gastric damage could be abolished by pretreatment of mice with IMC.[3]

In preliminary experiments we observed a protective effect of 16-16-dimethyl-PGE_2 in acetaminophen-(paracetamol) induced hepatitis in mice. These observations prompted us to investigate the effect of IL-1 on hepatic injury in this model. We measured the effect of IL-1α on mortality of recipients, serum transaminase levels, and the production of PGE_2 by hepatic tissue ex vivo. In one experiment we also measured the production of LTC_4, since IL-1 induces the synthesis of lipoxygenase products[16] and LTC_4 has been shown to have a protective effect in radiation-induced injury.[17]

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RESULTS

Prevention of AAP-Induced Mortality by IL-1: Dose Dependency

IL-1α was given i.p. in doses ranging from 37 to 9000 units/mouse (corresponding to 1850 to 450 000 units/kg or 6.15 to 1494.45 ng/kg) 2 h before intragastric administration of AAP (300 mg/kg). Figure 1 shows the survival of mice 48 h after AAP-administration. In comparison to control mice given saline, the survival of mice in all groups treated with IL-1α was better, but was statistically significant only with doses of 333, 1000 and 3000 U/mouse. Thus,

it appears that the effect of IL-1α reaches a plateau with doses between 333 and 1000 U/mouse, and that higher doses are less protective. Neither of these IL-1α doses were toxic for normal mice (data not shown).

Time Dependency of IL-1α Protective Effect

IL-1α was given i.p. in the dose of 1000 U/mouse 1, 2, 6, 12 or 24 h before AAP-administration. At each time interval a group of control mice were given saline. The survival of mice within 48 h is shown in Fig. 2. The survival of mice in control groups was between 25–30%. IL-1α increased the survival of mice regardless of the time of its administration. However, the significant increase in protection ($P < 0.05$) was seen when IL-1α was given 2 or more hours before AAP. At the 2 hour interval between IL-1α and AAP, the survival was 78% and did not change much by increasing this interval up to 24 h (maximal survival at 12 h interval; 90%). Administration of IL-1α 2 h after AAP had no any effect on survival of mice (data not shown).

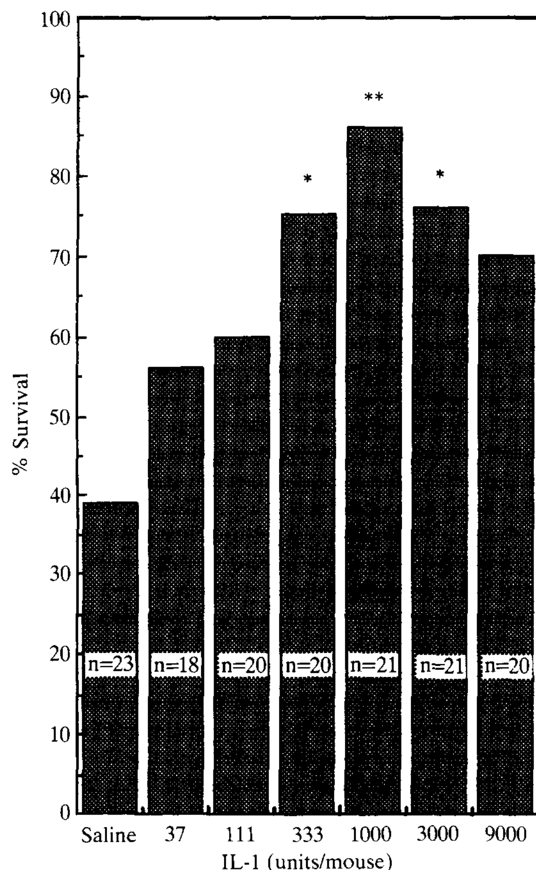

Figure 1. Influence of IL-1α on survival of mice with AAP induced hepatitis.

IL-α was given i.p. 2 h before AAP administration (300 mg/kg) and survival recorded after 48 h. $^*P < 0.05$; $^{**}P < 0.005$.

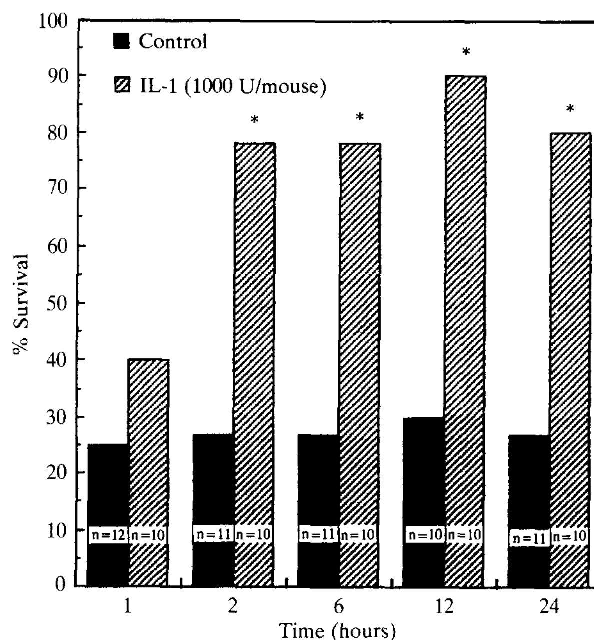

Figure 2. Time course of the protective effect of IL-1α.

Mice were injected i.p. with saline or IL-1α (1000 U/mouse) at indicated time intervals prior to oral administration of AAP. Survival was recorded 48 h later. $^*P < 0.05$.

Serum Transaminase Levels

Mice were given either saline or IL-1α (1000 U/mouse) 2 h before AAP. Twenty-four hours later, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were determined in plasma of 12 surviving mice in each group. At the same time baseline AST and ALT levels were determined in 19 normal mice. As shown in Table 1, the levels of both enzymes were considerably higher in mice given AAP than in normal mice (AST increased around 16-times and ALT 60-times). Pretreatment with IL-1α reduced the increase of transaminase levels 3–4 times ($P < 0.001$ in comparison to saline-treated mice).

IL-1α significantly decreased the number and size of necrotic foci in the liver, which could be easily seen

TABLE 1. Serum transaminase levels.

Treatment	AST (U/L)[b]	ALT (U/L)[b]
Normal mice	75 ± 4 (n = 19)	23 ±1 (n = 19)
Saline + AAP[a]	1230 ± 188 (n = 12)	1310± 172 (n = 12)
IL-1α + AAP[a]	347 ± 64* (n = 12)	487 ± 104* (n = 12)

[a] Saline or IL-1α were given i.p. 2 h before administration of AAP (300 mg/kg). [b]Determined 24 h after AAP administration; mean ± SEM, $^*P < 0.001$.

by macroscopic observation and histological analysis of the liver (data not shown).

Production of PGE_2 and LTC_4

Samples of normal liver and livers of AAP-administered mice pretreated with IL-1α or saline were incubated for 1 hour and amounts of PGE_2 and LTC_4 were determined in supernatants (Table 2). Livers of mice with hepatitis pretreated with saline produced 1.37 times more PGE_2 and about four times more LTC_4 than livers of normal mice (contrary to the production of PGE_2, the difference in production of LTC_4 was highly significant; $P < 0.001$). Pretreatment with IL-1 increased the production of PGE_2 about 1.7 times, but did not influence the synthesis of LTC_4 ($P < 0.005$ and $P < 0.05$, respectively, in relation to saline pretreated mice with hepatitis). The addition of IMC in vitro, significantly decreased the PGE_2 synthesis, but had no significant effect on LTC_4 synthesis.

Effect of Indomethacin on IL-1α Induced Protection

In order to investigate the effect of IMC on IL-1α protection, four groups of mice were given AAP. Two groups of mice received IL-1α (1000 U/mouse) 2 h before AAP. One group of mice received also IMC (4 mg/kg i.p.) 30 min before IL-1α. Two control groups received either saline or IMC alone before AAP. Figure 3 shows the survival of mice 48 h after AAP administration. Similar to the results of previous experiments, IL-1α had a significant protective effect (82% survived as opposed to 45% of the saline-treated mice). The administration of IMC before IL-1α slightly reduced the protective effect of IL-1α (68% survived). IMC alone slightly reduced the survival of mice in comparison to saline-treated mice (survival 37% vs. 45%; $P > 0.05$). Thus IMC reduced the protective effect of IL-1α only partially if at all.

TABLE 2. Influence of IL-1 on PGE_2 and LTC_4 production ex vivo

Treatment of mice	PGE_2 (pg/ml)[b]	LTC_4 (pg/ml)[b]
Normal mice	1417 ± 130	798 ± 159
Saline + AAP[a]	1950 ± 187[c]	3210 ± 162
IL-1α + AAP[a]	3400 ± 328*	3252 ± 410

[a]Saline or IL-1α were given i.p. 2 h before administration of AAP (300 mg/kg). [b]Determined 6 h after AAP administration; mean ± SEM (n = 6). [c]Production by the same samples in presence of IMC (10^{-5}) was 629 ± 33 pg/ml. *$P < 0.005$.

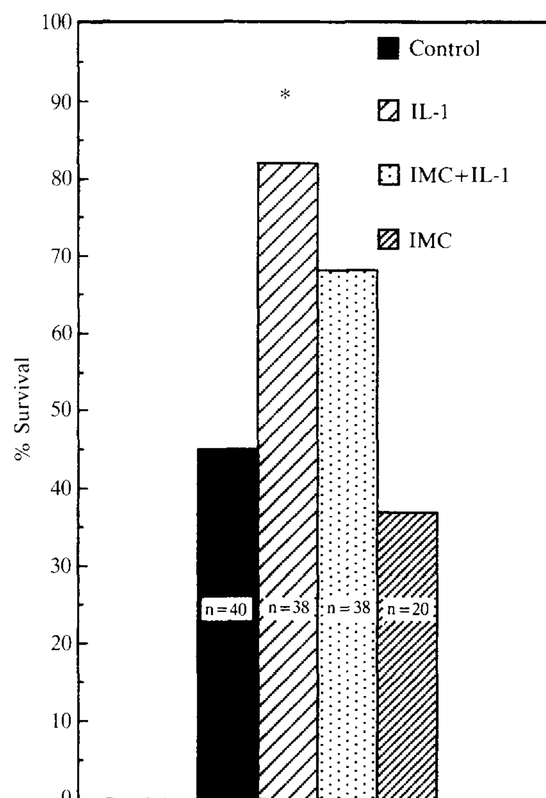

Figure 3. Effect of indomethacin on IL-1α induced protection.

Protective effect induced by a dose of 1000 U/mouse of IL-1α against AAP-hepatitis was reduced by prior treatment with indomethacin (4 mg/kg) administered i.p. 30 min before IL-1α. *$P < 0.05$.

DISCUSSION

Our results have clearly shown that IL-1α has a significant hepatoprotective effect. IL-1 reduced mortality as well as decreased the rise of transaminase level in mice with AAP-induced hepatitis. This protective effect was present only if IL-1 was given two or more hours before AAP. It was nearly maximal after a two hour interval and did not change much by increasing the time interval up to 24 h (Fig. 2). These data differ from data obtained when IL-1 was used in protection against radiation-induced hematopoietic damage, in which optimal protection was obtained when IL-1 was given 18–24 h before the damaging agent.[18] Also, in prevention of ethanol-induced gastric damage, IL-1 was maximally active when given 1 hour before ethanol,[3] although it had a protective effect if given five min to 15 h before the damaging agent.[4] These differences could be explained by different mechanisms of tissue damage, different agents and target tissues, and/or by different mechanisms of IL-1-induced protection in various models.

A very low dose of IL-1α (1000 U per mouse or 166

ng/kg) was maximally protective in our experiments (Fig. 1). In comparison to the protective effect of PGE_2 in the same model,[19] the protective effect of IL-1 on a weight basis was about 70 times stronger. This is in accordance with the results of Robert et al., who showed that IL-1 is one of the most potent cytoprotective agents used in prevention of ethanol-induced stomach toxicity.[3]

The mechanism of the IL-1 cytoprotective effect has not been much studied. One of the best known IL-1 effects is stimulation of PG synthesis.[7–9] Since PGE_2 has a cytoprotective effect on various tissues/cells, including protection of hepatic cells from AAP damage,[19] in our model we have investigated the production of this prostaglandin by liver tissue. Previous investigations have shown that a 6-hour interval between AAP administration and sampling of liver tissue is optimal for measuring of PG synthesis.[20] We also studied the production of LTC_4, since it was reported that IL-1 stimulates the synthesis of 5-lipoxygenase products,[16] and since LTC_4 has a cytoprotective effect in radiation-induced injury.[17] PGE_2 production by livers of non-treated mice with AAP-induced hepatitis was much higher than PGE_2 production by normal livers. Pretreatment with IL-1 more than doubled this production in AAP-treated mice (Table 2). On the other hand, the synthesis of LTC_4 in the same samples was not influenced by IL-1 pretreatment of mice. These results show that LTC_4 probably has no role in IL-1 mediated hepatoprotection.

If the IL-1 protective effect is mediated by endogenous PG-synthesis, then inhibitors of PG-synthesis should abrogate this effect. However, administration of indomethacin (4 mg/kg) before IL-1 had no significant effect on mortality protection by IL-1 (Fig. 3). These results differ from those obtained in IL-1 protection from ethanol-induced ulcers,[3] in which a similar dose of IMC (5 mg/kg), given before IL-1, abolished almost completely its protective effect. However, the inability of IMC to cancel the protective effect of IL-1 does not exclude the possible protective role of PG-s. Thus, as a non-specific inhibitor of prostanoid synthesis, IMC might also inhibit the synthesis of some hepatotoxic prostanoid which would decrease the hepatic injury.[20] A possible hepatotoxic prostanoid is thromboxane A2 (TxA2), which has been implicated in pathogenesis of LPS-induced toxicity[21] and ulcerative disorders in stomach.[22] However, such a role of TxA2 in pathogenesis of experimentally induced hepatitis has not as yet been clearly shown. Furthermore, IMC might have some pharmacological effects, not dependent on inhibition of PG-synthesis,[23] which could be protective for liver cells.

It is, however, possible that increased PGE_2-synthesis is only a side effect of IL-1-induced protection, which is mediated by independent mechanisms. In view of multiple biological effects of IL-1,[9] this assumption seems more realistic. It may be that IL-1 reduces the activity of drug metabolizing enzymes (cytochrome P-450) in liver[24] which then leads to a decrease in the rate of drug conversion to the active metabolite.[25] However, this mechanism was excluded in protection of cyclophosphamide hematopoietic toxicity.[2] Some investigators have shown that IL-1 induces synthesis of manganese sodium dismutase (Mn-SOD) in hepatic cells,[26] which may prevent oxidation injury during development of hepatitis.[27,28] Recently, a protective role of nitric oxide for LPS-induced hepatoxicity has been demonstrated.[29] It has also been shown that IL-1 and other cytokines stimulate synthesis of nitric oxide in hepatic cells.[30] Furthermore, IL-1 stimulates secretion of adrenal corticosteroids,[31] which induce synthesis of acute phase proteins.[32] Also, IL-1 induces synthesis of IL-6 by various cells[9,33] and this cytokine contributes to the radioprotective effect of IL-1 on hematopoietic cells.[34] Since IL-6 has important biological effects on the liver, e.g. stimulation of synthesis of acute phase proteins,[35,36] and induction of hepatic cell mitosis,[37] the mechanism of IL-1 stimulating IL-6 might also have a similar protective effect. Finally, IL-1 induces synthesis of cyclic adenosine phosphate (cAMP) and protein kinase activity,[33] which may lead to synthesis of protective and repair proteins.[38] This latter possibility is being presently investigated in our laboratory.

MATERIALS AND METHODS

Animals

CBA/H Zgr inbred mice were raised in an animal colony unit at the Department of Physiology. Mice of both sexes aged 11 to 16 weeks were used in the experiments. In particular experiments, mice of only one sex were used. They were maintained under standard laboratory conditions, fed with commercially available murine food pellets (K-1, Domžale, Slovenia) and allowed water *ad libitum*.

Chemicals

Pure AAP substance was a kind gift from the Krka pharmaceutical company (Novo Mesto, Slovenia). AAP was dissolved in heated PBS to which 1–2 drops of Tween 80 were added. Half ml of the resulting suspension was administered intragastrically. Recombinant human IL-1α (rh IL-1α) (117–271 Ro 24–5008; lot IL-1 2/88; sp act 3×10^8 U/mg) was kindly provided by Dr Peter Lomedico (Hoffmann-La Roche Inc.), by courtesy of Dr A. Marušić (Dept. Anatomy, School of Medicine, Zagreb). A stock solution of rhIL-1α was prepared in 0.2% BSA in pyrogen-free saline, aliquoted and stored at −70°C. It was diluted immediately before use and injected intraperitoneally in a volume of 0.2 ml. Control animals were given 0.2 ml pyrogen-free saline at the

same time. Indomethacin (Sigma Chemicals Co., St Louis, Mo.) dissolved in absolute ethanol, was injected at 4 mg/kg intraperitoneally.

Induction of Hepatitis with AAP

The procedure of Guarner et al.[20] was followed with slight modifications. To induce hepatic drug-metabolizing enzymes, mice were given phenobarbitone-sodium (Kemika, Zagreb) in drinking water during 7 days (0.3 g/L). Thereafter, mice were fasted overnight and AAP was given intragastrically, by a stomach tube, in a volume of 0.5 ml. Animals were allowed food 4 h later. In all experiments, a dose of 300 mg/kg AAP was administered, which induced 61%–73% mortality in control mice.

Plasma ALT and AST Concentrations

ALT and AST concentrations were measured 24 h after AAP administration. Plasma samples were obtained by a procedure in which haemolysis was undetectable. Mice were given 250 U heparin i.p. 15 min before bleeding. Blood was obtained by puncture of medial orbital angle with heparinized glass capillary tubes. Plasma was stored at −20°C for 24 h before transaminase determination. AST and ALT levels were determined by standard laboratory techniques.

Production Ex Vivo and Measurement of Eicosanoids

Samples of liver tissue, kept on ice, were minced in small fragments (1–2 mm^3) in phosphate buffered saline (PBS). After sedimentation at unit gravity, they were washed 2 times more in fresh PBS. The fragments were transferred into preweighed tubes and centrifuged at 500 g at +4 °C for 3 min. The sediment was quickly weighed and resuspended in Minimal Essential Medium (MEM, Gibco) (5 μl MEM per mg tissue) and incubated in a water bath at 37°C for 1 h. The samples were then centrifuged as above and supernatants stored at −70°C until analysis. Concentration of PGE_2 and LTD_4 in supernatants were determined by using appropriate RIA Kits (PGE_2 ^{125}I SPA system and LTC_4 ^3H TRK 800 system, respectively; Amersham, Herts UK), according to the manufacturer's instructions. The bound radioactivity was measured in a liquid scintillation counter.

Statistical Analysis

Results are expressed as mean ± SE. Parametric variables were compared by Student's t-test. Differences in survival between groups of mice were compared by chi-square test, using Yates's correction of the test when indicated.

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