Role of α_1-Antitrypsin and Detoxification Functions of the Liver in the Pathogenesis of Endotoxin-Induced Fever

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 130, No. 7, pp. 39-41, July, 2000
Original article submitted October 25, 1999

CCl_4-induced toxic damage to the liver in rats and rabbits is accompanied by inhibition of detoxifying functions of the liver and a decrease in plasma α_1-antitrypsin content and core body temperature. Injection of pyrogenal stimulated detoxifying functions of the liver, elevated α_1-antitrypsin content in the blood, and increased body temperature. Intravenous injection of α_1-antitrypsin caused hyperthermia. No pyrogenal-induced hyperthermia was observed in animals with CC_4-induced damage to the liver. These data indicate that functional activity of the liver and blood content of α_1-antitrypsin play an important role in the mechanisms of thermoregulatory reactions to endotoxin.

Key Words: *core body temperature; fever; α_1-antitrypsin; detoxifying function of the liver*

Previous studies demonstrated an interrelation between accumulation of endotoxin in the blood, symptoms of liver insufficiency, and the development of fever [4,8]. A correlation was found between functional activity of thermoregulatory structures in the brain and blood content of acute phase proteins synthesized by hepatocytes [1,7,8]. However, the role of the liver and hepatic endogenous proteinase inhibitors in the regulation of body temperature during fever received little attention.

Here we studied the role of detoxifying functions of the liver and hepatic proteinase inhibitors in the pathogenesis of endotoxin-induced fever.

MATERIALS AND METHODS

Experiments were performed on 10 male and female albino rats weighing 160-220 g and 12 rabbits weighing 2.5-3.5 kg. Experimental fever was induced by single injection of bacterial lipopolysaccharide from *S. typhi* (pyrogenal, N. F. Gamaleya Institute) to rabbits (0.5 μg/kg into the marginal ear vein) and rats (5 μg/kg intraperitoneally). Experimental toxic hepatitis was produced by single or 3-fold (with 24-h intervals) intragastric administration of 50% CCl_4 (oil solution) to rats and rabbits in doses of 5 and 2 ml/kg, respectively. Control animals received an equivalent volume of olive oil. Rectal temperature in rats and rabbits was measured at depths of 3 and 5 cm, respectively, using a TPEM-I electrical thermometer.

Plasma contents of α_1-antitrypsin (α_1-AT) and α_2-macroglobulin (α_2-MG) were measured as described elsewhere [3]. The severity of intoxication was evaluated by plasma level of medium-molecular-weight molecules (MWM) [5] and serum toxicity (ST) [6]. Detoxifying functions of the liver in rabbits were evaluated by the duration of narcotic-induced sleep (period from drug injection to the first spontaneous movement). Sodium thiopental in a dose of 30 mg/kg was injected into the marginal ear vein. Plasma content of urea was measured as described previously [2].

The results were analyzed by routine statistical methods.

RESULTS

Pyrogenal produced marked changes in the metabolism of plasma proteins, heat exchange, and detoxification functions of the liver. In rabbits, pyrogenal caused rapid and pronounced hyperthermia: 30, 60,

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0007-4888/00/0007-645$25.00

and 120 min postinjection the body core temperature increased by 0.5, 1.1, and 1.5°C ($p<0.05$). In rats, pyrogenal caused only moderate and delayed hyperthermia: body temperature increased by 1.1 and 1.0°C ($p<0.05$) 120 and 150 min postinjection.

Plasma contents of α_1-AT and α_2-MG in rats increased by 28.1 and 17.9%, respectively, 120 min after intraperitoneal injection of pyrogenal ($p<0.05$). In control rats, these parameters were 5.9±0.49 and 2.2±0.06 μmol/liter, respectively. The concentrations of α_1-AT and α_2-MG were calculated per 1 sec due to inhibition of the reaction [3]. Fever stimulated detoxification functions and urea formation in the liver. Plasma urea content in rabbits 60 and 120 min after the injection of pyrogenal increased by 48.7 and 81.3% (to 4.10± 0.78 and 5.3±0.6 μmol/liter, respectively, $p<0.05$). The time of narcotic-induced sleep at the peak of pyrogenal-induced hyperthermia in rabbits decreased by 23% (120 min after injection of pyrogenal, $p<0.05$).

Acute CCl_4-induced damage to the liver was accompanied by a decrease in plasma content of α_1-AT, inhibition of heat exchange, impairment of detoxifying functions of the liver, drop of body core temperature, and hypothermia. Rectal temperature in rabbits and rats decreased by 3.00±1.14 and 1.00±0.11°C, respectively, 24 h after CCl_4 poisoning and returned to normal 3-4 days postinjection. Hypothermia in rats was accompanied by a 50.8% decrease in plasma α_1-AT content ($p<0.05$), while the concentrations of α_2-MG and urea remained practically unchanged. The content of MWM in the plasma was 20% higher than in the control (2.9±0.2 μmol/liter, $p<0.05$). ST increased by 78% compared to the control ($p<0.05$). In control rats, plasma levels of total protein and α_1-AT were 49.30± 3.47 g/liter and 5.90±0.49 μmol/liter, respectively. The duration of narcotic sleep in rabbits 24 h after CCl_4 poisoning increased by 25% ($p<0.05$).

In rats and rabbits with CCl_4-induced damages to the liver, pyrogenal did not cause hyperthermia, but decreased the content of α_1-AT (by 41%, $p<0.05$) and increased plasma concentration of urea. The content of α_1-AT in rat plasma 60 min after pyrogenal administration was 3.78±0.44 μmol/liter. The concentration of MWM and ST were 23.1 and 121% above the control, respectively ($p<0.05$).

Thus, pyrogenal caused fever in intact animals, had no effect after single intragastric administration of CCl_4, and induced hypothermia after repeated (3-fold) administration of CCl_4 (Fig. 1).

Sixty and 120 min after administration of 0.3 mg/kg α_1-AT to rabbits (plasma content of α_1-AT considerably increased during pyrogenal-induced fever and decreased under conditions of CCl_4 poisoning accompanied by hypothermia) body temperature increased by 1.0 and 1.1°C, respectively ($p<0.001$).

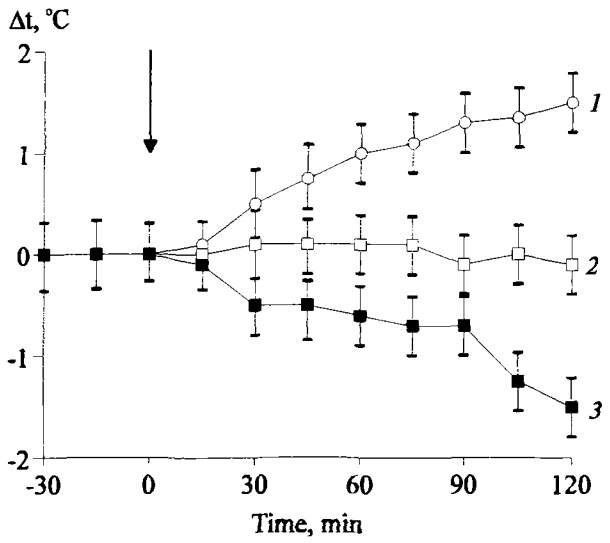

Fig. 1. Body temperature in rabbits with CCl_4-induced liver damage after intravenous injection of pyrogenal: control (2 ml/kg olive oil intragastrically, *1*), single (*2*), and 3-fold (*3*) intragastric administration of 2 ml/kg CCl_4 (50% oil solution).

These data suggest that functional state of the liver and blood content of α_1-AT play an important role in the mechanisms of thermoregulatory reactions to pyrogenal. Suppression of liver functions accompanied by a decrease in blood content of α_1-AT impairs typical thermoregulatory response of the body to pyrogenal and prevents the development of fever.

REFERENCES

1. F. I. Vismont, *Neuropeptides and Thermoregulation* [in Russian], Minsk (1990), pp. 50-66.
2. V. G. Kolb and V. S. Kamyshnikov, *Manual on Clinical Chemistry* [in Russian], Minsk (1982).
3. I. Yu. Koryagina, R. A. Zarembskii, and M. D. Balyabina, *Lab. Delo*, No. 2, 72-73 (1990).
4. D. N. Mayanskii, *Pat. Fiziol.*, No. 4, 80-86 (1985).
5. V. M. Moin, V. V. Nikolaichik, V. V. Kirkovskii, *et al.*, *Byull. Izobret.*, No. 41 (1989).
6. O. A. Rad'kova, G. A. Boyarinov, I. N. Balishina, and K. V. Krylov, *Ibid.*, No. 11 (1985).
7. B. Saad, K. Frei, F. A. Schobl, *et al.*, *Eur. J. Biochem.*, **229**, No. 2, 349-355 (1995).
8. F. I. Vismont, O. G. Shust, and E. N. Kuchuk, *Recent Advances in Thermal Biology*, Ed. V. N. Gourine, Minsk (1999), pp. 127-131.