A Uniform Alteration in Serum Lipid Metabolism Occurring during Inflammation in Mice

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ABSTRACT—The present study was designed to delineate changes in serum lipid levels following various kinds of tissue injury or inflammation such as contact sensitivity to picryl chloride, thermal burn, carrageenin-induced edema, the administration of turpentine oil, Freund's complete adjuvant (FCA), killed Bordetella pertussis (BP) or lipopolysaccharide (LPS). A uniform change in the serum lipid metabolism was observed in mice that received these inflammatory stimuli; that is, increases in total cholesterol, free cholesterol and phospholipid levels, a decrease in the ester ratio and a decline in lecithin: cholesterol acyltransferase activity as well as a decrease in albumin levels, which is an index of the acute-phase response. However, serum triglyceride levels were increased by treatment with the bacterial stimuli (FCA, BP and LPS) but decreased by treatment with the other stimuli. The serum free cholesterol and phospholipid levels were significantly correlated with the intensity of contact sensitivity, which was modified by treatment with cyclophosphamide. Indomethacin or dexamethasone suppressed carrageenin-induced edema and inhibited some of the alterations in lipid metabolism that developed during inflammation because each affected a part of the lipid metabolism. These findings suggest that, like the appearance of acute-phase proteins, the uniform change in serum lipid metabolism may be another sensitive index of the acute inflammatory response.

Many types of injuries, including bacterial and parasitic infection, mechanical and thermal trauma, tumor growth and ischemic necrosis, lead to the appearance in the blood of certain liver-produced plasma proteins known as acute-phase proteins (1). Svenson et al. (2, 3) have reported that human chronic inflammatory diseases, particularly rheumatoid arthritis, are characterized by an altered lipoprotein composition and metabolism as well as an acute-phase response in parallel with the inflammatory activity. In a previous study, we found that adjuvant-induced arthritis in rats, an animal model of rheumatoid arthritis, exhibits abnormal alterations in serum lipids during acute and chronic stages in the development of arthritis (4). Both stages display pronounced changes in plasma acute-phase proteins (5). Since some of these proteins interact with plasma lipoproteins which transport lipids (6, 7), such changes in plasma lipids may be another form of biochemical derangement developing in the mammal responding to acute inflammation or tissue injury as well as to chronic inflammation. Several studies have reported variations in the lipids during disorders promoting the acute-phase response (8–10); however, there has been no
systematic investigation on the lipid metabolism during inflammation.

The present study was undertaken to characterize the changes in serum lipids and related biochemical parameters when mice are subjected to various kinds of inflammation and to ascertain whether the occurrence of lipid abnormality is dependent upon the nature of the noxious stimulus.

MATERIALS AND METHODS

Animals and blood sampling
Male BALB/c mice were purchased from Japan SLC, Inc. (Hamamatsu) and used at 8 weeks of age. They were housed in a room that was air-conditioned (23 ± 2°C with 60 ± 10% humidity) and illuminated for 12 hr (7:00–19:00). The mice were given food pellets (MF, Oriental Yeast Co., Tokyo) and water ad libitum. In each experiment, the animals were made to fast for 15 hr prior to the collection of blood samples. The samples were taken from the orbital vein using a Pasteur pipet with the animal under ether anesthesia. The serum was separated by centrifugation (1500 × g for 10 min).

Drugs and chemicals
Picryl chloride (PCI), cyclophosphamide (CY), turpentine oil and adjuvant Bordetella pertussis (BP) were purchased from Nacalai Tesque, Ltd. (Kyoto); λ-carrageenin was from Wako Pure Chemical Ind., Ltd. (Osaka); lipopolysaccharide (LPS) from Escherichia coli 055:B5, Freund’s complete adjuvant (FCA) and Freund’s incomplete adjuvant (FIA) were from Difco Laboratories (Detroit, MI, U.S.A.); indomethacin and dexamethasone were from Sigma Chemical Co. (St. Louis, MO, U.S.A.).

Sensitization and elicitation of contact sensitivity
Contact sensitivity to PCI was induced according to a standard technique. Mice were sensitized to PCI by painting their shaved abdomens with 50 μl of 3% PCI in a 4:1 mixture of acetone: olive oil. Five days later, the mice were challenged by smearing 20 μl of 1% PCI in acetone: olive oil on the dorsal surface of both ears. Ear thickness of mice was measured with a dial thickness gauge (Peacock, Tokyo) before and 24 hr and 48 hr after challenge and expressed as the mean increase (%) above the values before challenge (ear swelling). Animals that were challenged but not sensitized were used as a negative control. In some experiments, CY, which was dissolved in saline immediately before use, was injected i.p. in a single dose of 200 mg/kg either 2 days before or 2 days after sensitization. Treatment with CY at different times was used to enhance or suppress contact sensitivity reactions (11, 12).

Inflammatory stimulus
Thermal, chemical or bacterial stimulus was used to elicit the acute inflammatory reaction in the mice. Thermal burn was created by pressing the footpads of both hind paws on a hot plate (60°C) for 30 sec under ether anesthesia. Carrageenin and turpentine oil are the most common chemical irritants. Carrageenin edema was induced by s.c.-injection of 0.05 ml of 1% λ-carrageenin in saline into the footpads of both hind paws. Turpentine oil was injected i.m. in a volume of 0.05 ml into the middle of each femoral muscle of the mice. Other animals were injected i.p. with 10 μg of LPS or 2 × 10⁹ heat-killed BP, or injected s.c. with 0.1 ml of an emulsion of equal volumes of saline and FCA (containing heat-killed Mycobacterium butyricum) or FIA by divided injection into the flank skin and footpads of the forelegs. The combination of BP with FCA has been used as an immunizing procedure for developing chronic arthritis in mice (13).

Analytical methods
Total and free cholesterol levels in the serum were fluoroenzymatically determined as described previously (14). Lechithin: cholesterol acyltransferase (LCAT) activity was obtained by measuring the rate of esterification of free cholesterol at 550 nm using 0.025 ml of serum, 0.05 ml of 3 mg/ml lechithin, 0.05 ml of 0.05 M Tris-HCl buffer (pH 8.4), and 0.05 ml of 0.02 M NaCl. After 1 hr at 37°C, the reaction was stopped by the addition of 1 ml of 0.6 M NaOH.
cholesterol in the serum, as described by Dieplinger and Kostner (15). The activity was expressed as the esterification rate of free cholesterol in serum per hour (%/hr). Triglyceride level was enzymatically determined by a commercial kit, Triglyceride E-test Wako (Wako Pure Chemical Ind.). Phospholipid level was determined by the method of Yoshi-da et al. (16). Albumin level was determined by a commercial kit, Albumin B-test Wako (Wako Pure Chemical Ind.).

Statistical analysis

The results obtained were expressed as the mean ± S.E. Student’s t-test for paired observations was used to test for significance.

RESULTS

Changes in serum lipid levels and LCAT activity following contact sensitivity reaction

The immunized mice (S + C group) showed maximum ear swelling at 24 hr after challenge, a 100% increase over the control (Fig. 1A). At this time, changes in the serum lipid metabolism also reached maximum; the mice displayed significant increases in the serum levels of total and free cholesterol and phospholipids together with a decline in LCAT activity (Fig. 1B). A major portion of the increased total cholesterol was free cholesterol. The non-immunized mice (C group), which were challenged but not sensitized, showed similar lipid changes but they were weaker than those of the immunized mice.

To determine whether the severity of inflammation is related to the degree of the serum lipid changes, the mice were injected i.p. with CY 2 days before or 2 days after sensitization with PCI. The contact sensitivity skin reaction was significantly augmented by pretreatment with CY and significantly suppressed by post-treatment with CY (Fig. 2A) which closely paralleled the findings of the serum free cholesterol and phospholipid levels (Fig. 2B). Figure 3 shows the correlation of the intensity of ear swelling with the free cholesterol level (Fig. 3A) and the phospho-

![Graphs and figures showing changes in serum lipid levels and LCAT activity following contact sensitivity reaction.](image-url)
lipid level (Fig. 3B) in the serum. A positive correlation was established between them (P < 0.01, respectively). In this experiment, administration of CY alone had little influence on the serum lipid metabolism.

Fig. 2. Effects of cyclophosphamide (CY) on picryl chloride (PCI)-induced contact sensitivity and serum lipid changes in mice. Animals were injected with CY (200 mg/kg, i.p.) either 2 days before (−2d) or 2 days after (+2d) sensitization with 3% PCI. Five days later, they were challenged with 1% PCI as detailed in Materials and Methods. Data represent the mean ± S.E. (n = 6) of ear swelling (A) and serum free cholesterol and phospholipid levels (B) at 24 hr after challenge. **P < 0.01, compared with the S + C group (challenged after sensitization but not treated with CY). Control: the non-treated control group.

Fig. 3. Correlation of free cholesterol level (A) and phospholipid level (B) in the serum with the intensity of contact sensitivity to picryl chloride in mice. All values were obtained from animals, except for those in the non-treated control group, in the experiment for Fig. 2. The solid line represents the linear regression equation obtained by least-squares analysis. r: correlation coefficient.
Effect of various inflammatory stimuli on serum lipid levels and LCAT activity

The severity of thermal burn and carrageenin-induced edema in the paws of the mice reached maximum after 3 hr and 5 hr, respectively. However, the degree of changes in the serum lipids and LCAT activity were greatest at 24 hr after the treatment, as found after injection with turpentine oil. Figure 4 shows the serum lipid levels and LCAT activity in mice at 24 hr after treatment with such injurious stimuli. The serum albumin level is also shown as an index of the acute-phase response. All stimuli elicited qualitatively similar alterations in the serum chemicals; that is, increases in free cholesterol and phospholipid levels, decreases in triglyceride and albumin levels and a decline in LCAT activity. Total cholesterol levels also increased concomitantly with free cholesterol.

Figure 5 shows the changes in the serum lipid and albumin levels and LCAT activity in mice injected with a bacterial adjuvant, i.e., FCA, BP or LPS. All animals treated showed serum changes very similar to those observed in the mice treated with the thermal or chemical stimulus described above except that the serum level of triglycerides increased reversely. However, FIA, which does not contain heat-killed bacteria, had no effect on the serum lipids and LCAT activity (data not shown).

Effects of indomethacin and dexamethasone on the changes in lipid and LCAT activity following carrageenin edema

Mice were injected s.c. with indomethacin (10 mg/kg) or dexamethasone (0.5 mg/kg) 30 min before injection with α-carrageenin into the footpads of the hind paws. Both antiinflammatory agents suppressed the development of carrageenin-induced edema (Fig. 6). Dexamethasone was more effective than indomethacin. Table 1 shows the effects of indomethacin and dexamethasone on the serum lipid and albumin levels and LCAT activity at 24 hr after carrageenin injection. Indomethacin significantly prevented the increases in the serum free cholesterol and phospholipid levels induced by carrageenin treatment, but did not prevent the decreases in the serum triglyceride and albumin levels and the decline

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**Fig. 4. Effects of thermal burn and chemical irritants on serum lipid levels, lecithin:cholesterol acyltransferase (LCAT) activity and albumin level in mice.** Animals received burn stress (60°C, 30 sec; Burn), s.c.-injection of 1 mg of carrageenin (Carr) or i.m.-injection of 0.1 ml of turpentine oil (Turp) as detailed in Materials and Methods. Data represent the mean ± S.E. (n = 6) of serum levels of biochemical parameters at 24 hr after treatment with each injurious stimulus. *p < 0.05, **p < 0.01, compared with the non-treated control group.
in LCAT activity. On the other hand, dexamethasone prevented the decreases in the serum triglyceride and albumin levels and the decline in LCAT activity, but did not prevent and rather enhanced the increases in the serum free cholesterol and phospholipid levels. To evaluate whether or not the antiinflammatory agent used per se affects the lipid metabolism, we determined the serum lipid and albumin levels and LCAT activity at 24 hr after injection with indomethacin or dexamethasone to the normal mice. The results given in Table 1 show that indomethacin caused a significant decline in LCAT activity and decreases in the serum triglyceride and albumin levels, whereas dexamethasone caused significant increases in the serum free cholesterol and phospholipid levels.

Fig. 5. Effects of bacterial adjuvants on serum lipid levels, lecithin:cholesterol acyltransferase (LCAT) activity and albumin level in mice. Animals were injected with Freund’s complete adjuvant (FCA) (0.05 ml), Bordetella pertussis (BP) (2 × 10⁹) or lipopolysaccharide (LPS) (10 µg) as detailed in Materials and Methods. Data represent the mean ± S.E. (n = 6) of serum levels of biochemical parameters at 24 hr after treatment with each adjuvant. *P < 0.05, **P < 0.01, compared with the non-treated control group.

Fig. 6. Inhibitory effects of indomethacin (IND) and dexamethasone (DEX) on carrageenin-induced paw edema in mice. Animals were injected s.c. with 0.05 ml of 1% λ-carrageenin in saline into the footpads of both hind paws (Carr control) and treated with IND (10 mg/kg, s.c.) or DEX (0.5 mg/kg, s.c.) 30 min before injection with carrageenin. Non-treated control animals were injected with only saline. Data represent the mean ± S.E. (n = 6) of footpad swelling. *P < 0.05, **P < 0.01, compared with the Carr control group. ○: Non-treated control, ●: Carr control, ▲: Carr + IND, ■: Carr + DEX.
Table 1. Effects of indomethacin (IND) and dexamethasone (DEX) on serum lipid levels, lecithin:cholesterol acyltransferase (LCAT) activity and albumin level in normal and carrageenin (Carr)-treated mice

| Treatment                | Free cholesterol (mg/100 ml) | Phospholipids (mg/100 ml) | Triglycerides (mg/100 ml) | LCAT (%/hr) | Albumin (g/100 ml) |
|--------------------------|------------------------------|---------------------------|---------------------------|-------------|-------------------|
| Normal animals           |                              |                           |                           |             |                   |
| Non-treated control      | 28.2 ± 1.5                   | 195 ± 8                   | 98.0 ± 7.6                | 12.55 ± 1.00| 3.53 ± 0.05       |
| IND                      | 27.9 ± 1.4                   | 185 ± 15                  | 83.2 ± 18.0              | 7.41 ± 1.23*| 3.05 ± 0.18       |
| DEX                      | 36.9 ± 1.3**                 | 256 ± 5.5**               | 124.8 ± 10.7            | 12.73 ± 1.04| 3.53 ± 0.09       |
| Carrageenin-treated animals |                          |                           |                           |             |                   |
| Carr control             | 37.3 ± 1.1                   | 250 ± 3                   | 69.1 ± 9.5               | 4.15 ± 0.42 | 3.29 ± 0.05       |
| Carr + IND               | 32.6 ± 0.9**                 | 196 ± 7.2**               | 55.8 ± 11.2             | 4.91 ± 2.25 | 3.11 ± 0.07       |
| Carr + DEX               | 46.5 ± 1.2                   | 289 ± 6                   | 80.9 ± 7.6*              | 9.55 ± 1.23**| 3.47 ± 0.05*     |

Animals were injected s.c. with 0.05 ml of 1% β-carrageenin into the footpads of both hind paws (Carr control) and treated with IND (10 mg/kg, s.c.) or DEX (0.5 mg/kg, s.c.) 30 min before injection with Carr. Normal animals were treated with saline (Non-treated control), IND or DEX alone. Data represent the mean ± S.E. (n = 6) of serum levels of biochemical parameters at 24 hr after treatment. *P < 0.05, **P < 0.01, compared with the respective control group.

DISCUSSION

The results presented here demonstrate that a uniform change in the mouse serum lipid metabolism occurs regardless of the inflammatory stimulus, i.e., whether it is contact sensitivity, thermal injury, chemical irritants, killed bacteria or LPS. The results are summarized in Table 2; the data show increases in the levels of total cholesterol, free cholesterol and phospholipids, a decrease in the ester ratio (the ratio of cholesteryl ester to total cholesterol) and a decline in LCAT activity as well as a decrease in the level of albumin, which is an indicator for the acute-phase response (1). However, the triglyceride level was either increased by the bacterial stimuli or decreased by the other stimuli used. It has been demonstrated that animals injected with live bacteria or bacterial endotoxin (LPS) develop massive hypertriglyceridemia (17, 18). This rise in serum triglyceride levels is related to the depressed tissue lipoprotein lipase activity (19, 20). Thus, the action of BP and FCA

Table 2. Summary of changes in the serum biochemical parameters in mice that received various inflammatory stimuli

| Injury or stimulus        | TC       | FC       | CE/TC    | PL       | TG       | LCAT     | ALB      |
|--------------------------|----------|----------|----------|----------|----------|----------|----------|
| Contact sensitivity      | ↑        | ↑        | ↓        | ↑        | ND       | ↓        | ND       |
| Thermal burn             | ↑        | ↑        | ↓        | ↑        | ↓        | ↓        | ↓        |
| Carrageenin              | ↑        | ↑        | ↓        | ↑        | ↓        | ↓        | ↓        |
| Tarpentine oil           | ↑        | ↑        | ↑        | ↑        | ↑        | ↓        | ↓        |
| M. butyricum (FCA)       | ↑        | ↑        | ↑        | ↑        | ↑        | ↓        | ↓        |
| B. pertussis             | ↑        | ↑        | ↑        | ↑        | ↑        | ↓        | ↓        |
| Lipopolysaccharide       | ↑        | ↑        | ↑        | ↑        | ↑        | ↓        | ↓        |

TC: total cholesterol, FC: free cholesterol, CE: cholesteryl ester, PL: phospholipids, TG: triglycerides, LCAT: lecithin:cholesterol acyltransferase, ALB: albumin, FCA: Freund’s complete adjuvant, ↑: significant increase, ↑: tendency to increase, ↓: significant decrease, ↓: tendency to decrease, ND: not determined.
used in this study also appears to be exerted by mechanisms similar to LPS. Therefore, in mice treated with each bacterial stimulus, the specific hypertriglyceridemic effect may overcome the hypotriglyceridemic effect that would be essentially developed during the inflammatory reaction.

The characteristic changes in the serum lipid metabolism reported in this study appear to be a sort of general inflammatory response. Similar patterns of serum lipid changes, including the low levels of triglyceride, have been observed in the chronic phase of adjuvant arthritis in rats (4). Furthermore, increases in plasma levels of cholesterol and phospholipids as well as triglycerides have been reported in rats injected with LPS (20) and in rabbits injected with croton oil (21). In addition, a lower activity in plasma LCAT, which is considered the enzyme responsible for the formation of the serum cholesteryl ester, has also been seen in monkeys treated with LPS (22) and in humans during the acute phase reaction (23).

In the experiment of contact sensitivity to PCl using CY in mice, we found a significant correlation between the serum lipid levels and the intensity of ear swelling (Fig. 3). This supports the presence of a strong influence of the inflammation activity on serum lipid metabolism, at least regarding free cholesterol and phospholipid levels. Modulation of the immune response by suppressor T cells may have some role in the mechanisms (12).

The exact mechanisms by which various inflammatory stimuli produce a uniform change in lipid metabolism could not be defined by these experiments, but they may occur through the induction of individual factors. Possible factor candidates are cytokines and glucocorticoids because they are secreted following tissue injury and play important roles in the inflammatory process (24–27) and also because regulatory communication exists between them (28). A number of cytokines, including interleukin-1, interleukin-6 and tumor necrosis factor, also affect the production of acute phase proteins in the liver (25, 29, 30) and lipid metabolism (31). In preliminary studies, we found that s.c.-injection of rats with some interleukins results in changes closely resembling the characteristic series of lipid metabolism changes described above (32). Thus, one or more cytokines seem to affect the lipid and lipoprotein metabolism in a manner analogous to the acute-phase protein production.

When carrageenin-induced edema in mice was suppressed by indomethacin or dexamethasone, some of the alterations in serum lipid metabolism was inhibited (Table 1), because each drug individually affected a part of the lipid metabolism; dexamethasone increased the levels of serum free cholesterol, phospholipids and triglycerides, whereas indomethacin tended to decrease the levels of triglycerides and albumin, and reduced the LCAT activity. It has been demonstrated that administration of glucocorticoids can cause hyperlipidemia (33). Therefore, all these findings suggest that glucocorticoids are also partly involved in the lipid metabolism changes during the inflammatory response as discussed above.

The uniform change in serum lipid metabolism observed in this study seems to be another sensitive index, in addition to acute-phase proteins, of the active state of acute inflammation, although the possibility that such changes in lipid levels may occur under other pathological conditions related to impaired liver function cannot be eliminated. Further research is needed on the pathophysiological role of these lipid changes in acute inflammation and on the identification of the injury-derived mediators involved in the regulation of acute-phase lipids or lipoproteins. This should provide insight into the complex acute-phase reaction in inflammation.

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