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Experimental Uveitis Induced by Intravitreal or Intravenous Lipoteichoic Acid in Rabbits

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Purpose: To investigate the role of lipoteichoic acid (LTA), one of the cell wall components in Gram-positive bacteria in uveitis.

Methods: Intraocular inflammation in rabbit eyes was induced by intravitreal or intravenous injections of LTA from *Staphylococcus aureus* or *Streptococcus sanguis*. The inflammation was monitored progressively with the laser flare-cell photometer, and examined by periodic clinical observations. Histological examinations were performed 24 hours after administration, and aqueous protein concentrations and cell counts were also determined.

Results: Intraocular inflammation appeared within 6–9 hours of LTA intravitreal injection, became maximal at about 24–48 hours postinjection, and lasted for nearly 6 days. Intraocular inflammation was also induced by intravenous injection of LTA at a higher dose. Inflammation reached a peak 4–5 hours after injection, and rapidly disappeared in 24 hours. No cellular response was observed in intravenous LTA-treated eyes.

Conclusions: This study demonstrates that LTAs from Gram-positive bacteria have the biological activity to induce intraocular inflammation in rabbits by intravitreal or intravenous injection. Therefore, we suggest that LTA may play a role in the pathogenesis of uveitis as one of the etiological factors. **Jpn J Ophthalmol 1999;43:368–374**

Key Words: Intravenous injection, intravitreal injection, laser flare-cell photometer, lipoteichoic acid, rabbit, *Staphylococcus aureus*, *Streptococcus sanguis*.

Introduction

Gram-positive bacteria is involved in the pathogenesis of endophthalmitis. In a recent study of an endophthalmitis model inoculated with pneumococci, tumor necrosis factor (TNF)-α was detected in the intraocular specimens. Intravitreal steroid therapy was also confirmed to have an effect on inflammation, because of the decrease in the production of TNF-α.[1] This indicates that certain cellular components of Gram-positive bacteria are effective in inducing inflammation by stimulating cytokine production. Furthermore, some clinical reports reveal that patients with Behçet's disease (BD) have a significantly higher incidence of tonsillitis and dental caries, in which certain strains of streptococci are involved.[2] *Streptococcus sanguis* is proposed as a potential agent in BD, based on higher isolation rates, skin reactivities, and antibody titers in patients than in controls.[3,4] These results suggest that certain serotypes of *S. sanguis* may play roles in the pathogenesis of BD.

Systemic or intraocular administration of an endotoxin, lipopolysaccharide (LPS), a component of Gram-negative bacterial outer membranes, induces an acute anterior uveitis known as endotoxin-induced uveitis (EIU).[5] It has been hypothesized that EIU may serve as a model for the human uveitis associated with Gram-negative bacterial infection, such as ankylosing spondylitis and Reiter's syndrome. However, the pathogenic effects of Gram-positive bacteria on ocular inflammation have been less extensively investigated. Peptidoglycan and muramyl dipeptide

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(MDP), the cell wall components present in both Gram-positive and Gram-negative bacteria, are confirmed to be able to induce intraocular inflammation in rabbits.[6,7] However, the uveitogenic cell wall component specific to Gram-positive bacteria has not yet been identified in detail.

Lipoteichoic acid (LTA) is a component of the cell membrane of a variety of Gram-positive bacteria. It mediates many of the toxic and metabolic effects in Gram-positive infections and has a variety of biological activities,[8] including antigenicity,[8,9] adherence to host tissue,[9,10] induction of collagenase and prostaglandin synthesis,[11] mitogenicity,[8,11] complement activation, as well as release of cytokines such as TNF-α, interleukin (IL)-1 β, IL-6, and IL-8.[12,13] In a recent study, we demonstrated that LTA from *Staphylococcus aureus* induces intraocular inflammation in the rat.[14] In this study, we report an experimental uveitis model in the rabbit induced by administration of LTA derived from *S. aureus* or *S. sanguis*. Intraocular inflammation was induced in rabbits by intravitreal or intravenous injection of LTA. The kinetics of inflammation in the anterior chamber (AC) were monitored at periodic intervals with a laser flare-cell photometer.[15,16]

Materials and Methods

Animals

Dutch pigmented rabbits of either sex, weighing 1.5–2.0 kg, were purchased from Saitama Experimental Supply, and housed in the animal care facilities. Animals were fed with standard laboratory chow and maintained in the standard light:dark cycle.

LTA and Experimental Materials

LTAs, phenol extracts of *S. aureus* or *S. sanguis*, were purchased from Sigma Chemical Co. (St. Louis, MO, USA). They were suspended in sterile physiological saline solution at different concentrations, filtered through sterile 0.2-μm filters, and prepared for animal administration. All dilutions were made shortly before injection. Before administration, rabbits were anesthetized by intramuscular injection of a solution (1 mL/kg) containing a 2:1 mixture of chlorpromazine hydrochloride (5 mg/mL; Shionogi Pharmaceutical, Osaka) and ketamine hydrochloride (50 mg/mL; Sankyo Pharmaceutical, Tokyo). Topical anesthesia was done with 0.4% proparacaine hydrochloride ophthalmic solution (Benoxil; Santen Pharmaceutical, Osaka). Mydriasis was achieved with topical application of 0.5% tropicamide and 0.5% phenylephrine hydrochloride (Mydrin P; Santen) 30 minutes before measurement by laser flare-cell photometer.

LTA Administration

The uveitogenic activity of LTA in rabbits was examined by two routes: Intravitreal injection and intravenous injection.

Intravitreal Injection

LTA from *S. aureus* or *S. sanguis* was diluted for injection unilaterally in experimental eyes. The concentration of LTA ranged from 0.1–10 μg per 10 μL. After anesthesia had been administered to the rabbits, 10 μL of LTA was injected into the center of the vitreous body at the pars plana about 2.5 mm posterior to the limbus, with a 30-gauge needle attached to a Hamilton syringe (Hamilton, Reno, NV, USA). Care was taken to avoid traumatizing the lens during injection. In the contralateral eyes, 10 μL of sterile saline was injected in the same manner, as control. At least 4 rabbits (4 eyes) were included in each group of experimental or control animals.

Intravenous Injection

In the experimental group, LTA from *S. aureus* or *S. sanguis* was adjusted to 0.25 to 2.5 mg/mL, and given intravenously through a marginal ear vein at a dose of 1.0 mL/kg. As control, 1.0 mL/kg of sterile saline was given in the same way. At least 3 rabbits (6 eyes) were included in each group of animals.

Measurement of Flare

After LTA administration, flare measurement was determined to study the kinetics of inflammatory response in the AC at periodic intervals, using a laser flare-cell photometer[15,16] (FC-1000; Kowa, Tokyo).

Clinical Observation

A clinical investigation was performed at periodic intervals using a slit-lamp microscope (SL-5D; Topcon, Tokyo). The fundus was also observed by indirect ophthalmoscopy (EB-110S; Neitz, Tokyo).

Protein Concentration and Cell Number in Aqueous Humor

Paracentesis was undertaken 24 hours after LTA administration. Aqueous humor (AH) was pooled and immediately mixed with 5% ethylenediaminetetraacetic acid (EDTA) in the proportion of 9:1 to prevent protein clotting. The inflammatory cells in AH were counted using an improved Neubauer

Jpn J Ophthalmol
Vol 43: 368–374, 1999

hemocytometer (EKDS, Tokyo). Aqueous protein concentration was measured by the method of protein assay described by Bradford[17] (Bio-Rad Labs, Richmond, CA, USA).

Pathology

Twenty-four hours after LTA administration, 4 animals were sacrificed by an overdose injection of sodium pentobarbital (Nembutal; Abbott, Osaka) through a marginal ear vein. Eyeballs were enucleated immediately, and fixed in 10% formaldehyde solution for more than 24 hours. Sections were stained with hematoxylin-eosin (H-E) for histopathological examination.

Statistical Analysis

All data were expressed as mean ± standard error of mean (SEM), and statistical comparison was made using the Student *t*-test. A P value of $<.05$ was considered significant.

Results

Intravitreal Injection

Quantification of aqueous flare intensity. Different doses (0.1, 0.3, 1, and 3 μg) of LTA from *S. aureus* or those (1, 3, and 10 μg) from *S. sanguis* were injected intravitreally into rabbit eyes. In experimental eyes injected with *S. aureus* LTA, aqueous flare appeared within 6–9 hours after injection, reached a peak at about 24 hours, and gradually disappeared in 6 days (Figure 1). *Staphylococcus aureus* LTA produced elevated aqueous flare values of 82.6 ± 34.9, 724.8 ± 180.5, 912.7 ± 125.2, and 475.5 ± 69.3 photon count/ms at 24 hours after intravitreal injection, with doses of 0.1, 0.3, 1, and 3 μg, respectively. One microgram of *S. aureus* LTA produced higher flare intensity than the larger dose of 3 μg.

In intravitreal *S. sanguis* LTA-treated eyes, similar inflammatory kinetics were noted, but the flare intensity with a 1-μg dose was much weaker than in *S. aureus* LTA-treated eyes (Figure 2). With different doses of 1, 3, and 10 μg of *S. sanguis* LTA, aqueous flare intensity was significantly elevated to 235.7 ± 107.7, 328.9 ± 77.4, and 644.0 ± 164.6 photon count/ms at 24 hours after administration. Flare count increase was not observed in the contralateral eyes injected with saline. The maximum flare intensity in the AC was less than 12.7 ± 10.5 photon count/ms.

Clinical observation. The LTA-induced uveitis was clinically characterized by acute iridocyclitis, consisting of conjunctival hyperemia, iris and ciliary injection, miosis, presence of cells, and flare in the anterior and posterior chambers (Figure 3A). Fibrin deposits were present diffusely 6–9 hours after intravitreal injection, became maximal, and began to coalesce along the pupillary margin within 24–36 hours. Inflammation in the AC reached a peak at about 24–48 hours and gradually decreased at 1 week. In high-dose LTA-injected eyes, posterior subcapsular cataract was a complication.

In high-dose LTA-injected eyes, uveitis signs were also found in the fundus 24 hours after LTA injec-

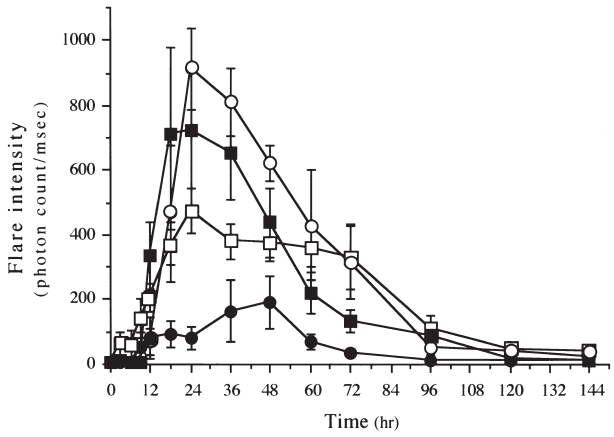

Figure 1. Kinetics of aqueous flare counts in uveitis induced by intravitreal injection of *Staphylococcus aureus* LTA (mean ± SEM; n = 4). Aqueous flare intensity appeared within 6–9 hours after injection, reached peak at about 24 hours, and gradually disappeared in 6 days. ●: 0.1 μg; ■: 0.3 μg; ○: 1.0 μg; □ 3.0 μg.

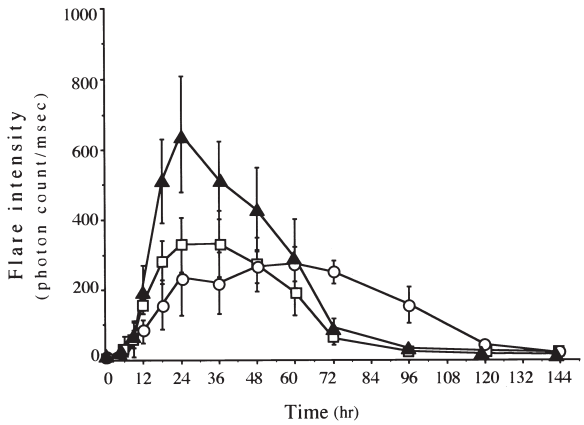

Figure 2. Inflammatory kinetics of aqueous flare intensity in uveitis induced by intravitreal injection of *Streptococcus sanguis* LTA (mean ± SEM; n = 4). Aqueous flare intensity increased to reach peak at about 24 hours, showing a dose-dependent response. ○: 1.0 μg; □: 3.0 μg; ▲: 10 μg.

tion, including choroidal exudate, blot retinal hemorrhage, retinal vascular dilatation, and vitreous opacity. (Figure 3B). Vitreous opacification initially appeared 24 hours after intravitreal injection, maximized within 48–72 hours, and lasted for more than 1 week. In some serious cases, massive vitreous gliosis could result. There was no relapse within the first 2 weeks of the observation period.

Protein determination and cell counts. To confirm the intraocular inflammation induced by LTA, paracentesis was performed 24 hours after intravitreal injection of a 1-μg dose of *S. aureus* LTA or a 10–μg dose of *S. sanguis* LTA. The results are demonstrated in Figure 4. In the experimental eyes receiving 1 μg of *S. aureus* LTA or 10 μg of *S. sanguis* LTA, similar aqueous protein concentrations of 29.1 ± 3.8 and 23.1 ± 2.5 mg/mL were produced (n = 4), which was significantly greater than the value in the control eyes (0.13 ± 0.05 mg/mL, $P < .01$). However, as for the cell counts, 1 μg of *S. aureus* LTA and 10 μg of *S. sanguis* LTA produced a cell value of 737.5 ± 108.2 and 1240 ± 172.7/mm^3 (n = 4, $P < .01$), respectively. There was a twofold difference in cell count between these two groups.

Histopathology. The inflammation was characterized by polymorphonuclear leukocyte and monocyte infiltration (Figure 5). A dense noncellular exudate filled both the anterior and posterior chambers. Iris congestion, ciliary injection, and lymphocyte infiltration in the ciliary body were observed. In some serious cases, anterior peripheral synechia was also found.

Intravenous Injection

Quantification of aqueous flare intensity. Intraocular inflammation was also induced in the rabbit by intravenous injection of *S. aureus* LTA at a dose of 0.25 mg/kg or *S. sanguis* LTA at a dose of 2.5 mg/kg, which was nearly 100–1,000 times higher than the effective dose of LPS (2.5 μg/kg). As a result, the increase in aqueous flare intensity promptly reached a peak 4–5 hours after intravenous injection, and lasted for only 24 hours (Figure 6). The highest flare intensity of 194.1 ± 71.6 or 48.8 ± 23.0 photon count/ms was produced with a dose of 0.25 mg/kg of *S. aureus LTA or 2.5 mg/kg of S. sanguis* LTA (both: n = 6). *Streptococcus sanguis* LTA failed to produce an increase of flare intensity at a dose of 0.25 mg/kg. An increase of flare value was not observed in the saline-injected rabbits ($P < .01$).

Clinical observation. The clinical manifestations were bilateral bulbar and palpebral conjunctival hyperemia and superficial ciliary injection. Miosis and

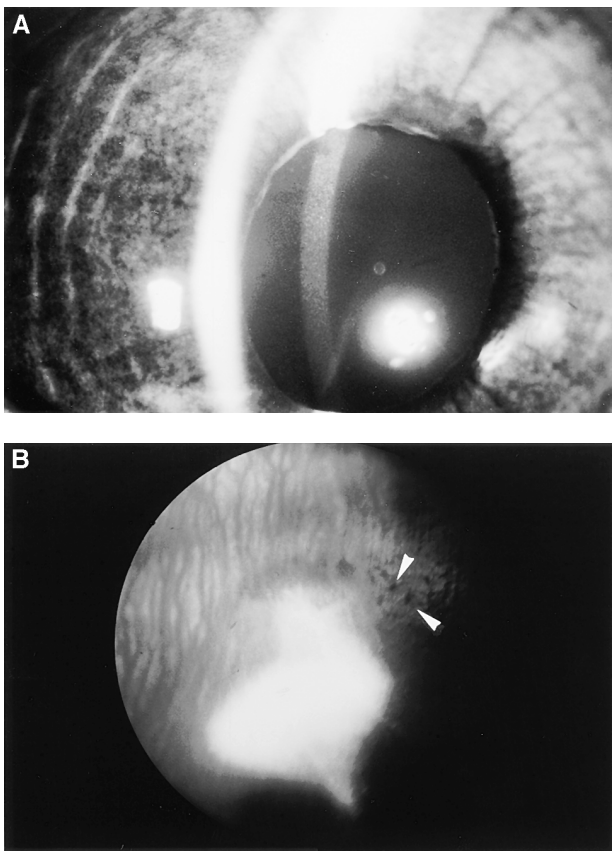

Figure 3. (**A**) Slit-lamp microphotograph of anterior chamber of experimental eye 24 hours after intravitreal injection of *Streptococcus sanguis* LTA, showing myosis, moderate flare, and cells. (**B**) Blot retinal hemorrhage (arrowheads) and choroidal exudate in fundus of high-dose LTA-treated eye.

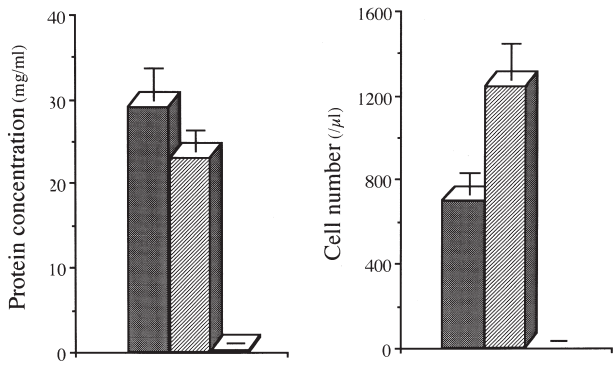

Figure 4. Protein concentrations and cell numbers in aqueous humor 24 hours after LTA intravitreal injection (mean ± SEM; n = 4). ■: *Staphylococcus aureus* 1.0 μg; ▨: *Streptococcus sanguis* 10 μg; □: saline.

Jpn J Ophthalmol
Vol 43: 368–374, 1999

a moderate flare response in the AC were prominent signs 4 hours after the intravenous injection of LTA. No cellular response was observed.

Histopathology. Four animals were sacrificed for histopathological study 4 hours after intravenous injection. There were no remarkable histological findings after LTA administration. In the ciliary body, moderate vascular congestion was demonstrated without any leukocyte infiltration.

Discussion

In this study, we developed an uveitis model in the rabbit by local or systemic administration of LTA. Our results revealed that LTA had an uveito-pathogenic effect to induce intraocular inflammation in the rabbit. The kinetics of the intraocular inflammation induced by LTA from *S. aureus* and *S. sanguis*, showed a pattern similar to EIU[6,18,19]: intraocular inflammation was initiated within 3–6 hours, reached its maximum at 24 hours after intravitreal injection, and disappeared gradually in 1 week. Pathological findings were also similar to those observed in EIU: an acute inflammation consisting of neutrophils and mononuclear cells infiltrating in the anterior and the posterior segments of the eye without evidence of vasculitis.[20] To assess the possibility that the uveitogenic effects of LTA in our test were due to LPS contamination, the LPS activity in LTA preparations was determined by the Limulus test.[14] Endotoxin concentrations in LTA solutions were in a low range, 10^{-4} times lower than LTA itself. Therefore, the inflammatory effects of LPS can be considered to be negligible in our data. Additionally, CD14, one of the LPS-binding receptors, has been reported to be responsive to LTA.[21] This suggests that LPS and LTA may share a common pathway for inflammatory induction by the same cytokine production.

Injection of *S. aureus* LTA resulted in a stronger intraocular inflammation in the rabbit. Also in our previous LTA studies in the rat model, *S. aureus* LTA administration produced a stronger ocular inflammation than *Streptococcus*-derived LTA.[14] Similar uveitogenic divergences in LTA obtained from a variety of bacteria have been revealed in different species of experimental animals. The reasons for these divergences are still unknown. It has been re-

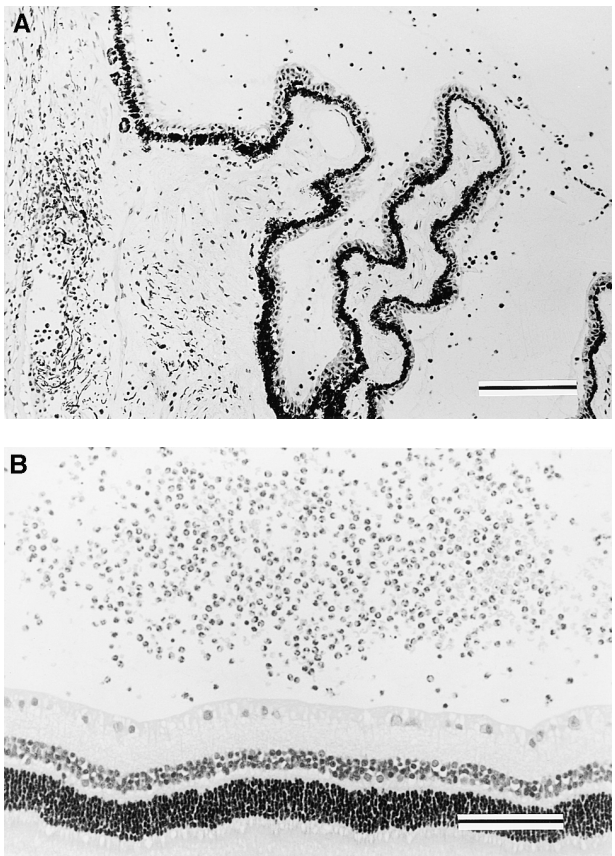

Figure 5. (**A**) Histopathological section (hemotoxylin-eosin stain) from experimental eye 24 hours after intravitreal injection of *Staphylococcus aureus* LTA demonstrating vasodilation and neutrophil infiltrations in ciliary body. Moderate cellular infiltration is evident in posterior chamber (×30, Bar = 700 μm). (**B**) Vitreous cavity in same eye. Neutrophils and monocytes infiltrate vitreous body (×66, Bar = 300 μm).

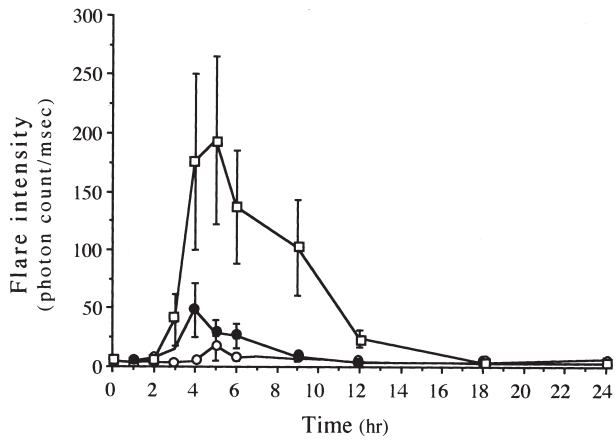

Figure 6. Time course of aqueous flare counts in uveitis induced by intravenous injection of LTA (mean ± SEM; n = 6). Mild intraocular inflammation was induced by intravenous injection of *Staphylcoccus aureus* LTA at dose of 0.25 mg/kg. This increase in aqueous flare intensity promptly reached a peak at 4–5 hours, and lasted for only 24 hours. □: *S. aureus* 0.25 mg/kg; ●: *S. sanguis* 2.5 mg/kg; ○: *S. sanguis* 0.25 mg/kg.

ported that the magnitude and characteristics of some of these uveitogenic activities vary according to the origin of the LTA.[13,22,23] Certain molecular structural differences or any intraspecies variations in the LTA derived from a wide variety of bacteria may explain our results.

In intravitreal *S. sanguis* LTA-treated eyes, the degree of inflammation correlated with the injected dose. In intravitreal *S. aureus* LTA-induced eyes, flare intensity also increased in a dose-dependent manner up to 1 μg, but not 3 μg. The reason was not clear. Cousins et al[24] described a dose-independent response in uveitis induced by LPS intravenous injection. It is hypothesized that capillary leak can be initiated and inhibited by the same mediators, and that the greater levels of mediators released by higher doses of endotoxin act to inhibit vascular permeability. Additionally, the greater systemic hypotensive effect of the higher endotoxin dose would further reduce the intravascular hydrostatic pressure and result in a lower flare measurement. In our data, intravitreal injection of a high dose of LTA was also thought to have an effect on vascular permeability inhibition. Therefore, this dose-dependent phenomenon might be explained by positive and negative feedback effects of the production of certain inflammatory mediators.

Our data showed interestingly that 1 μg of *S. aureus* LTA produced an increase in aqueous protein concentration of similar magnitude as 10 μg of *S. sanguis* LTA, whereas it was less effective in inducing leukocyte infiltration, producing only half the cell count as compared to 10 μg of *S. sanguis* LTA. This evidence indicates that intravitreal *S. aureus* LTA causes strong intraocular inflammation by elevating the uveal vascular permeability, but fails to induce an immunocellular response. In contrast, *S. sanguis* LTA was considerably effective in inducing cellular infiltration. Bhakdi et al[22] has reported that in vitro *S. sanguis* LTA has the ability to stimulate the production of IL-1β, IL-6, and TNF-α in cultured human monocytes, whereas *S. aureus* LTA fails in this stimulatory efficacy. The differences in cytokine profile induced by LTAs may cause the difference in cellular infiltration of these two LTAs.

In our experiment, intravenous injection of LTA was also performed to induce an anterior uveitis in rabbits. After intravenous injection with a high dose of LTA, a moderate flare increase was produced in the AC, reached a peak after 4–5 hours, decreased rapidly, and persisted for only 24 hours. The time-course of LTA-induced uveitis was also similar to that observed in EIU.[24–26] As Howes et al[26] and Kufoy et al[27] described, in EIU, noncellular infiltration in the AC was induced by intravenous injection of LTA in rabbits. Both cytological examination of AH and histological observation failed to confirm the presence of inflammatory cells. *Staphylococcus aureus* LTA showed more potent uveitogenic effects than *S. sanguis* LTA, when administered locally or systemically.

Intravenous injection of 2.5 μg of *Salmonella typhimurium* LPS could increase the aqueous flare reading to as high as 324 photon count/ms in our study (unpublished data). Whereas, only 194 photon count/ms of flare intensity was induced with an intravenous dose of 250 μg/kg of *S. aureus* LTA. With this dose, intravenous injection of *S. sanguis* LTA failed to elicit intraocular inflammation in the rabbit, but induced a slight inflammatory response with a high dose of 2,500 μg/kg. Therefore, LTA is less active than LPS in inducing uveitis in vivo.

In conclusion, our experiments demonstrate that intravitreal injection or intravenous injection of LTA, a cell wall component of Gram-positive bacteria, can induce intraocular inflammation in the rabbit. The inflammatory kinetics and histopathological changes induced by LTA closely resemble those observed after LPS application. We suggest that Gram-positive bacteria may play an important role in the pathogenesis of uveitis as one of the etiological factors.

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Jpn J Ophthalmol
Vol 43: 368–374, 1999

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