Irreversible Photoreceptors and RPE Cells Damage by Intravenous Sodium Iodate in Mice Is Related to Macrophage Accumulation

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The retinal pigment epithelial (RPE) cells phagocytose the shed, lipid-rich photoreceptor outer segments that form the blood-retinal barrier and play an important role in maintaining the integrity of the retina. In addition, the RPE cells transport nutrients and metabolites to the retina, recycle retinoids, and play critical roles in maintaining retinal homeostasis. Thus, a dysfunction of the RPE can lead to retinal diseases such as age-related macular degeneration (AMD) and photoreceptor degeneration. AMD is a degenerative retinal-choroidal disease and the leading cause of blindness in the elderly in developed countries. Exudative AMD is characterized by choroidal neovascularizations, and nonexudative AMD is characterized by geographic atrophy of the RPE. A determination of the pathological mechanisms involved in the development of AMD is necessary to be able to treat it effectively.

Sodium iodate (NaIO3), a stable oxidizing agent, can damage the RPE cells selectively. NaIO3 converts glycine to potentially toxic glyoxylate in the melanocytes of the RPE cells, and it also inhibits the activity of some enzymes in RPE cells. The NaIO3-induced retinchoroidal degeneration is used as an animal model of nonexudative AMD because the progression of damage is similar to that observed in patients with nonexudative AMD. In patients with nonexudative AMD, a dysfunction of the RPE leads to the death of the photoreceptor cells and, similarly, exposure of RPE cells to NaIO3 results in their death followed by secondary damage of the photoreceptors. Thus, determining the mechanism causing the RPE and photoreceptor degeneration should provide clues on the development of nonexudative AMD.

Many researchers have reported on the time- and dose-dependent changes in the NaIO3-induced retinal degeneration. The RPE degeneration induced by NaIO3 leads to the production of pigment-rich substances, and both the thickness of the photoreceptor outer and inner segments and the outer nuclear layer are reduced. In addition, exposure of the RPE cells to NaIO3 induces a loss of the integrity of the RPE cells and an enlargement of RPE cells. Although a dysfunction of the RPE cells leads to a reduction in vision, the time-dependent changes in the RPE morphological and physiological changes have not been determined.

Thus, the purpose of this study was to determine the progression of the morphological and physiological alterations induced by an intravenous injection of NaIO3. To accomplish this, we recorded fundus photographic and tomographic images, determined the morphological changes in the RPE histologically, measured the retinal blood flow by laser speckle flowgraphy (LSFG), and the physiology of the retina by
electroretinography after an intravenous injection of NaIO3 in mice.

**Materials and Methods**

**Animals**

All experiments were performed in accordance with the Association for Research in Vision and Ophthalmology (ARVO) Statement on the Use of Animals in Ophthalmic and Vision Research. The procedures were approved and monitored by the Institutional Animal Care and Use Committee of Gifu Pharmaceutical University. Male, 8- to 12-week-old C57BL/6J mice (Japan SLC, Hamamatsu, Japan) were used for this study. The mice were raised under controlled lighting conditions (12:12 light:dark) with free access to standard diet (CLEA Japan) and tap water.

**Sodium Iodate (NaIO3)-Induced Retinal Degeneration**

The NaIO3 was injected intravenously in mice that were anesthetized by an intramuscular injection of a mixture of ketamine (80 mg/kg; Daiich-Sankyo, Tokyo, Japan) and xylazine (6 mg/kg; Bayer, Health Care Osaka, Japan). The NaIO3 (Sigma-Aldrich Corp., St. Louis, MO, USA) was dissolved in phosphate-buffered saline (PBS), and the mice were injected with 20 mg/kg or 40 mg/kg of NaIO3 through a tail vein. The control mice were injected with the same volume of PBS.

**Optical Coherence Tomography (OCT)**

OCT images were recorded on days 0, 1, 5, 7, 14, 21, and 28 after the intravenous NaIO3 injection. The images were obtained with the Micron IV fundus camera and an OCT Scan Head equipped with a mouse objective lens (Phoenix Research Labs, Pleasanton, CA, USA). The OCT images were taken after anesthesia by a mixture of ketamine and xylazine. The pupils were dilated by 5 % of topical 0.5% tropicamide and 0.5% phenylephrine hydrochloride (Mydrin-P; Santen Pharmaceuti-

**Histological Analyses**

Histological analyses were performed on retinal cross sections stained with hematoxylin and eosin (H&E). After cervical spine dislocation, the eyes were enucleated and immersed in a fixative solution containing 4% paraformaldehyde (PFA) for at least 24 hours at 4°C. Paraffin-embedded sections of 5 μm were cut through the optic disc of each eye, processed in a standard manner, and stained with H&E. Images were taken of the stained sections with a fluorescent microscope (BX-9000; Keyence, Osaka, Japan) of 3 areas at about 500 μm (central), 1000 μm (middle), and 1500 μm (peripheral) from the optic nerve head.

**Immunohistochemistry**

After removing the cornea, lens and retina from the enucleated eyes, eight radial cuts were made on the isolated eyecups. The RPE-eyecups were flat mounted and prepared for immunohis-

**TUNEL Staining**

TUNEL staining was performed according to the manufacturer’s protocol (In Situ Cell Death Detection kit; Roche Biochemicals, Mannheim, Germany) to detect apoptotic cells. For this, the retinal sections were rinsed in PBS three times and incubated with 0.1% sodium citrate aqueous containing 0.1% Triton X-100 for 10 minutes. They were then placed in the TUNEL reaction mixture, 10% terminal deoxyribonucleotidyl transferase (TdT) enzyme solution diluted in fluorescein–dUTP mixture solution, at 37°C for 1 hour. The sections were washed in PBS three times at room temperature. Three sections of each eye were photographed, and the number of TUNEL-positive cells in the RPE and ONL was counted at 300–700 μm from the optic disc. The average of the counts in the three images was used as the number of TUNEL-positive cells/eye.

**Fluorescein Angiography**

Seven days after the NaIO3 injection, fluorescein angiography was performed with the Micron IV Retinal Imaging Microscope.
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system. After anesthesia and dilation of the pupils, 0.1 ml of a 1% fluorescein-saline solution (Alcon Pharmaceuticals, Tokyo, Japan) was injected intravenously, and fluorescein angiograph-ic images were recorded after 1 minute.

Electroretinography (ERGs) were recorded on days 7, 14, 21, and 28 after the NaIO3 injection. Mice were maintained in a completely dark room for 24 hours and then anesthetized with a mixture of ketamine (80 mg/kg) and xylazine (6 mg/kg) and their pupils dilated. Flash ERGs were recorded from the left eye of each dark-adapted mouse by placing a gold-ring electrode (Mayo, Aichi, Japan) in contact with the cornea, and the reference electrode (Nihon Kohden, Tokyo, Japan) inserted into the tongue. The ground electrode (Nihon Kohden) was inserted subcutaneously near the tail. All procedures were performed under dim red light, and the mice were kept on a heating pad to maintain a constant body temperature during the ERG recordings. The amplitude of the a-wave was measured from the a-wave trough to the b-wave peak, and the b-wave was measured from the baseline to the trough of the b-wave.

Blood Flow Analysis

Laser speckle flowgraphy (LSFG; Softcare, Iizuka, Japan) was used to measure the retinal blood flow as described in detail. This device consisted of a fundus camera equipped with a halogen lamp and a diode laser (λ_max = 830 nm; maximum output power, 1.2 MW). The laser pattern was photographed by a video camera (435 pixels by 435 pixels) at a rate of 50 frames/second. The measured fundus area was 435 × 435 pixels (width × height), with an estimated depth of tissue penetration of 0.5 to 1 mm. Illumination with the laser light creates a speckle pattern due to the random interference of the laser light in the illuminated area. LSFG software was used to compute the mean blur rate (MBR) offline, which is closely related to blood flow velocity. Mean of vessel area and tissue area and all retinal area were measured.

Real-Time Polymerase Chain Reaction (PCR)

Mice were euthanized by cervical spine dislocation, and the eyes were quickly removed. The retinæ were carefully isolated from the eyes and RPE complex were rapidly frozen in liquid nitrogen. The RNA was extracted from the RPE complex with the High Pure RNA Isolation kit (Roche Diagnostics, Tokyo, Japan), and the RNA concentration was determined spectrophotometrically at 260 nm. First-strand cDNA was synthesized in a 10-µL reaction volume with the Prime Script RT reagent kit (Perfect Real Time; Takara, Shiga, Japan). The expression of the gene was quantified by real-time PCR with the SYBER Premix Ex Taq (Takara) and a TP 8000 Thermal Cycler Dice Real Time systems (Takara). The PCR primer sequences used were:

- retinal G protein coupled receptor (Rgr)
  - Forward: 5'-CTCCTGACCACATCTTCTCTTTG-3' and Reverse: 5'-GGTGCAGTATGTGATGATAACG-3',
  - HtrA serine peptidase 1 (Htra1)
  - Forward: 5'-GATCCGAATGATGTCGCTCACA-3' and Reverse: 5'-ATTTCCTTGGCCGCCCTGCG-3',
  - complement component 3 (C3)
  - Forward: 5'-AGCACAGCTACATAGTCAGGC-3' and Reverse: 5'-GATTTAGCTTTGTTGGGCTG-3',
  - glyceraldehyde-3-phosphate dehydrogenase (Gapdh)
  - Forward: 5'-TGTGTTCCCTGCTGCTGACG-3' and Reverse: 5'-TTGCTGTGGAACTGCGAG-3',
  - Monocyte chemotactic protein-1 (Mcp-1)
  - Forward: 5'-CTGACCAGCTTCTCTCTTCTTTG-3' and Reverse: 5'-CGGCGCAGACACATGACA-3',
  - intercellular adhesion molecule 1 (Icam-1)
  - Forward: 5'-GGGCTGTTGCTGAGACG-3' and Reverse: 5'-ATACACGGTGATGAGCGG-3',
  - interleukin-6 (Il-6)
  - Forward: 5'-TGAGAGAGGACCTCATCCAGT-3' and Reverse: 5'-TCTGCAACTGATCCAGTT-3',
  - interleukin-1β (Il-1β)
  - Forward: 5'-AACCTGCAGTGTGATGACG-3' (forward) and Reverse: 5'-CAGCAACGGAGCCTTTTGTTTG-3'.

Macrophage Depletion

To deplete the macrophages in the retina, 10 µg/g body weight of clodronate liposomes (FormuMax Scientific, Inc., Palo Alto, CA, USA) was injected intraperitoneally 24 hours before the NaIO3 injection, and 5 µl/g body weight of clodronate liposomes was injected 4 days after the NaIO3 injection as described in detail. Control mice were injected with the same volume of PBS.

Statistical Analyses

Statistical analyses were performed with the Statistical Package for the Social Sciences 15.0 J for Windows software (SPSS Japan, Inc., Tokyo, Japan). Data are presented as the means ± standard error of the means (SEM). The significance of the differences in the values was determined by Dunnett’s tests and Bonferroni tests. A P value <0.05 was taken to be statistically significant.

RESULTS

Time-Dependent Changes in Fundus and OCT Images of Murine Retinas After Intravenous NaIO3 Injection

To determine the time-dependent changes in the murine retina after an intravenous injection of NaIO3, OCT images were taken on days 0, 1, 5, 7, 14, 21, and 28 after the NaIO3 injection. The results showed that 20 mg/kg of NaIO3 caused a partial and transient damage to the retina while 40 mg/kg of NaIO3 initially damaged the RPE cells and then subsequently the ONL thickness at 5 days (Figs. 1A–D). Moreover, TUNEL staining showed that the death of the photoreceptors adjacent to the RPE cells. 8

Intravenous injection of PBS or 20 mg/kg NaIO3. That said, an injection of 40 mg/kg NaIO3 led to a loss of the integrity of the RPE with aggregation of the melanin granules in the RPE cells.
Figure 1. Changes in the optical coherence tomographic (OCT) images of NaIO$_3$-treated murine retinas with increasing time after the intravenous injection of sodium iodate (NaIO$_3$). (A–D) OCT images at 28 days after the intravenous injection and thickness of IS/OS + RPE, ONL, and retinal layer during 28 days after PBS (control), and after 20 or 40 mg/kg NaIO$_3$ injection. The thickness of the IS/OS + RPE was measured from the yellow to the
at 7 and 28 days. In addition, the inner and outer segments of the photoreceptors were not present (Fig. 2).

To examine the RPE tight junctions, the flat-mounted sections were immunostained for ZO-1, a component protein of the tight junctions between RPE cells. With 20 mg/kg NaIO₃ injection, the RPE border structures appeared disrupted at day 3 and worse on day 7. However, they had recovered at day 28, and the retina and RPE appeared normal (Fig. 3C). In contrast, after 40 mg/kg of NaIO₃, the integrity of the RPE was lost, and the degree of disruption was greater at 3 days and aggregation of the melanin granules was seen from 7 days to 28 days (Fig. 3D).

The permeability of the RPE barrier was evaluated by fluorescein angiography at 7 days after the NaIO₃ injection. The retinal vasculature was normal without dye leakage in the control mice and after the 20 mg/kg NaIO₃ injection on day 7. On the other hand, 40 mg/kg NaIO₃ led to leakage of fluorescein (Fig. 3E). These findings indicated that the integrity of the RPE and the blood-retinal barrier were not permanently altered by the injection of 20 mg/kg of NaIO₃ but were permanently disrupted at 7 days after 40 mg/kg of NaIO₃ was injected.

**Retinal Physiology After NaIO₃ Injection**

ERGs were recorded to determine the physiological condition of the retina after the NaIO₃ injection. Both the a- and b-wave amplitudes were significantly reduced at 7 days after 20 and 40 mg/kg NaIO₃ injection (Fig. 4). The amplitudes of both waves had recovered by 14 days after 20 mg/kg NaIO₃ but was still present at 28 days after 40 mg/kg of NaIO₃ (Fig. 4).

**Identifying Aggregated Particles in RPE by Immunostaining**

Immunostaining was performed to determine the components of the aggregation in the RPE cells. We examined the expression of RPE65, a protein expressed in the retinal pigment epithelial cells. The retinas of the mice that received 40 mg/kg NaIO₃ showed a reduction in the expression of RPE65 relative to that of the PBS-injected and the 20 mg/kg NaIO₃-injected retinas (Fig. 5A). Immunostaining for iba-1 and F4/80 indicated that the aggregated cells were macrophages observed after the 40 mg/kg NaIO₃ injection (Figs. 5B, 5C).
Retinal Blood Flow After NaIO3 Injection

The changes in the retinal blood flow with time were examined by LSFG. Our results showed that the blood flow was not changed until 28 days after 20 mg/kg NaIO3 injection compared with PBS (control) injection. In contrast, 40 mg/kg NaIO3 injection showed a significant reduction of the blood flow rate. In addition, 40 mg/kg NaIO3 decreased the mean of vessel area, mean tissue area, and mean area of the retina to
Changes in Expression of Genes Associated With AMD in NaIO3-Treated Mice

To confirm that the NaIO3-induced retinal degeneration had similar characteristics as those with AMD, the genes associated with AMD were assessed by RT-PCR. The expressions of the mRNA transcripts of Htra1 and C3 were significantly upregulated after the injection of 40 mg/kg NaIO3 compared to that in the control group (Figs. 7A, 7B). The expression of the mRNA transcripts of Rgr was markedly downregulated by 40 mg/kg NaIO3 injection compared to that of the control group (Fig. 7C).

Involvement of Macrophages in Retinal Damage After NaIO3 Injection

To determine whether macrophages were involved in the pathophysiology of the NaIO3-induced RPE and retinal damages, we investigated the expression of the genes related to macrophages by RTPCR. The expressions of the mRNA transcripts of Mcp-1 and Icam-1 were significantly upregulated compared to that in the control group at 1 day after the injection of 40 mg/kg NaIO3. Then, the expressions of the mRNA transcripts of H-6 and H-1β were upregulated at 3 days after the 40 mg/kg NaIO3 injection (Fig. 8A). We also examined the effects of clodronate, a chemical agent inducing macrophage apoptosis leading to macrophage depletion.27  Histological analysis revealed that the ONL thickness was decreased in NaIO3-injected group compared to that in control group. Depletion of the macrophages by the clodronate liposome prior to the NaIO3 injection suppressed the NaIO3-induced ONL thinning compared with NaIO3-injected group (Figs. 8B, 8C). However, the retinal function was not changed significantly by the depletion of the macrophages (data not shown). Additionally, the morphology of RPE was altered and aggregations were present in the flat mounts in the vehicle and the combined NaIO3 and clodronate injected group (data not shown).

DISCUSSION

The results showed that 40 mg/kg body weight of intravenous NaIO3 led to irreversible damage to the RPE and photoreceptors of mice. In addition, the results showed that macrophages were involved in the secondary loss of the photoreceptors after the NaIO3 injection.

A number of studies have investigated the retinal changes after different doses and routes of application of NaIO3.11,13,22

![Time course of NaIO3 injection](https://arvojournals.org/)

**Figure 4.** Amplitudes of the dark-adapted ERGs after the NaIO3 injection. (A) Typical dark-adapted ERGs measured at 7, 14, 21, and 28 days in the control, and the 20 and 40 mg/kg NaIO3 injection groups. (B) Amplitudes of the a- and b-waves at 7, 14, 21, and 28 days after the NaIO3 injection as control, 20, and 40 mg/kg NaIO3 groups. The intensity of the stimulus flashes varied from −2.92 to 0.98 log cd/m². Data are the means ± SEMs. n = 5 or 6. *P < 0.05, **P < 0.01 versus control group (Dunnett’s test).
Consistent with the results of earlier studies, H&E and ZO-1 staining showed that the RPE morphology was completely disrupted, and aggregations of cells were formed (Figs. 2–3). Immunostaining for Iba-1 and F4/80 showed an accumulation of macrophages around the RPE cells after the 40 mg/kg NaIO₃ injection (Fig. 5). However, an injection of 20 mg/kg NaIO₃ led to transient changes in the RPE as seen in the RPE flat mounts. We suggest that determining the differences between the reversible and irreversible changes will provide clues on the key factors causing the NaIO₃-induced damages. Unexpectedly, ZO-1 immunostaining of the RPE flat mounts showed that the morphology of RPE was disrupted, and there was aggregation of melanin granules surrounded by ZO-1 positive cells after the 40 mg/kg NaIO₃ injection (Fig. 3). Injection of 40 mg/kg also damaged the inner and outer segments of the photoreceptor and it leads to alterations of the ERGs (Fig. 2). Combining these results showed that the visual function was retained after a disruption of the RPE cells, but it was permanently impaired when aggregation of ZO-1 positive cells was present after the RPE morphology was altered (Fig. 4).

The blood-retinal barrier was disrupted 7 days after the 40 mg/kg NaIO₃ injection (Fig. 5). In patients, degeneration of the RPE after RPE tears and diabetic retinopathy led to a reduction of visual function. These findings strongly support the hypothesis that visual dysfunction is caused by the morphological and physiological damages of RPE. In nonexudative AMD patients, the reduction of the visual acuity is caused by degeneration of the RPE cells; however, evidence for an association between the morphology of the RPE and visual function has not been obtained in these AMD patients.

It has been reported that NaIO₃ injury mimicked non-exudative AMD, including the fundus, OCT, and histological characteristics. In addition, the results of this study showed that the retinal blood flow was decreased after the NaIO₃-induced RPE atrophy, similar to AMD pathology. Moreover, the expressions of the mRNA transcripts of Htra1, C3, and Rgr associated with AMD were altered after the
NaIO₃-induced retinal degeneration. Among all genetic factors, Htra1 has been reported to have the most influence on AMD. In addition, the results of earlier studies have suggested that C3 was associated with AMD, and the presence of the exon-skipping variant of Rgr in humans may contribute to the progressive degeneration in AMD. These results suggest that the NaIO₃ model is suitable to examine the pathophysiology of nonexudative AMD. Moreover, the results suggest that the ZO-1 aggregations in RPE cells might also be found in AMD patients.

C3 increased the activation of the complement pathway, which plays a major role in AMD pathogenesis. In addition, it is well known that complement component C3 is produced by macrophages and causes inflammation in AMD patients. The injection of NaIO₃ increased both the expression of the mRNA transcripts of Icam-1, which activates the adhesion of monocytes and that of Mcp-1, which induces the expression of macrophages at day 1 (Fig. 8). It was found that iba-1-positive and F4/80-positive macrophages migrated and accumulated around the melanin aggregations in the RPE cells.

**Figure 6.** Retinal blood flow determined by laser speckle flowgraphy (LSFG) is decreased after NaIO₃ injection. (A) Representative images of blood flow in control, and 20, and 40 mg/kg NaIO₃ injection groups at 28 days. Quantification data of blood flow for the mean of the vessel area (B), mean of the tissue area (C), and mean area of the all retina (D). Data are the means ± SEMs. n = 8 to 10. *P < 0.05, **P < 0.01 versus control group (Dunnett’s test).

**Figure 7.** Expression of AMD-related genes 7 days after NaIO₃ injection were evaluated by real-time PCR analysis. Htra1 (A) and C3 (B) mRNA transcripts expression are increased after the intravenous injection of 40 mg/kg NaIO₃ injection. (C) The expression of Rgr mRNA transcript is decreased in 40 mg/kg NaIO₃ injection. Data are the means ± SEMs. n = 4 to 6. **P < 0.01 versus control group (Dunnett’s test).
FIGURE 8. Involvement of macrophages in NaIO3-induced retinal degeneration model. (A) The expressions of macrophage-related genes were evaluated at 1, 3, 5, and 7 days after the NaIO3 injection by real-time PCR analysis. The expressions of Mcp-1, Icam-1, Il-6, and Il-1β mRNA transcripts were increased after the intravenous injection of 40 mg/kg NaIO3. (B) Representative photographs of H&E stained retinal sections in control, clodronate, NaIO3, and NaIO3 with clodronate injection groups. Scale bar: 50 μm. (C) Thickness of the outer nuclear layer at 7 days after the NaIO3 injection. Data are the means ± SEMs. n = 5 to 10. *P < 0.05 versus control, **P < 0.01 versus control; *P < 0.05 versus NaIO3; **P < 0.01 versus NaIO3 (Bonferroni test).
observed in the H&E stained sections after the 40 mg/kg NaIO3 injection (Figs. 2, 5). As a result, RPE cell death was caused at 12 hours after the 40 mg/kg NaIO3 injection (Fig. 1E). The results of earlier studies have suggested that the NaIO3 injection induced macrophage accumulation in the retina, 5,43 and the macrophages phagocytose the melanin aggregations.45 In addition, the expressions of the mRNAs transcripts of IL-1β and IL-6, inflammatory cytokines induced from macrophages, increased at 3 days after the 40 mg/kg NaIO3 injection (Fig. 8). The RPE morphology degenerated, and the thickness of the photoreceptors decreased 3 days and 5 days after the 40 mg/kg NaIO3 injection (Figs. 3D, 1C). These findings suggest that monocytes infiltrated the RPE and increased the expression of inflammatory cytokines after the RPE is injured.48 The results of earlier studies show that the infiltrating macrophages are important mediators of photoreceptor cell loss by the activation of inflammomasomes.49 Therefore, we conclude that macrophages are involved in the irreversible morphological changes in the RPE cells and photoreceptors through IL-6 and IL-1β. Additionally, our findings show that the depletion of macrophages suppressed the NaIO3-induced ONL thinning without RPE changes (Figs. 8B, 8C). These findings indicate that macrophages are deeply involved in the photoreceptor cell death in the NaIO3-induced model. Macrophage depletion could possibly restore visual function by recovering or transplantation of RPE cells if the nuclei of the photoreceptor cells were still present. Therefore, it is necessary to find factors that directly prevent the degeneration of RPE cells, and RPE transplantation might be effective for nonexudative AMD patients. Although the components of the aggregations in the RPE flat mounts in the NaIO3 model were not conclusively determined, it was confirmed that the aggregations were not macrophages in the immunostaining study of ocular cryosections. Our data suggest that macrophages did not induce the RPE injuries, but the RPE degeneration may have induced the migration and accumulation of the macrophages. Thus, it is expected that investigating the aggregation around RPE is important for understanding the progression of the NaIO3 injury.

In conclusion, the NaIO3-induced RPE and retinal degeneration model may be a suitable animal model to study nonexudative AMD. The present results show that macrophages are involved secondarily in the damage of the photoreceptor cells. We suggest that the differences between the reversible and irreversible changes may be a clue for developing therapeutic agents for nonexudative AMD.

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