Platelet-Activating Factor and Laser Trauma of the Iris

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Local application of platelet-activating factor (PAF) on the rabbit eye caused a dose-dependent significant increase in intraocular pressure (IOP). After laser irradiation of the iris the IOP showed a hypertensive phase of about 3 hr. Prophylactic treatment with the PAF antagonist BN 52021 but not with indomethacin abolished the hypertensive phase. Elevated levels of protein (10.6 ± 0.9 g/l) and prostaglandin E2 (PGE2, 1.7 ± 0.2 ng/ml) were measured in the aqueous humor 2 hr after laser irradiation of the iris. Prophylactic treatment with BN 52021 showed lower levels of protein (6.1 ± 0.7) and PGE2 (1.1 ± 0.02); with indomethacin pretreatment the level of protein was 3.4 ± 0.7 g/l and of PGE2, 0.10 ± 0.02 ng/ml. A role of PAF as a mediator in ocular inflammatory response is suggested. Invest Ophthalmol Vis Sci 30:1101-1103, 1989

Increased IOP is a serious possible postoperative complication following argon laser trabeculoplasty.1,2 Prednisolone,3 flurbiprofen4,5 and indomethacin6 cannot prevent this postoperative inflammatory rise in IOP. Possibly, other mediators than the products of the arachidonic acid cascade may be involved in this response.

Platelet-activating factor (1-O-alkyl-2-acetyl-glycero-3-phosphocholine, PAF) is the most potent inducer of platelet aggregation and has a wide spectrum of biological activities as a mediator of inflammation, increasing vascular permeability and edema, and causing leukocyte chemotaxis.7 Specific PAF antagonists, ginkgolides isolated from a Ginkgo biloba extract, are now available, interfering with receptors for PAF.7

The current study demonstrates that PAF may cause an elevation in IOP and that in a rabbit model of iris laser irradiation prophylactic treatment with the PAF antagonist BN 52021 prevents a rise in IOP and protects against breakdown of the blood-aqueous barrier.

Materials and Methods

Animals

Male pigmented rabbits (Chinchilla) weighing at least 2 kg, were sedated by intramuscular injection (0.75 ml/kg body weight) of Hypnorm (Duphar, Amsterdam, The Netherlands), containing 10 mg fluanisone and 0.2 mg fentanyl base per ml; local anesthesia was obtained by 0.2% oxybuprocain eyedrops. The animal investigations conformed to the ARVO Resolution on the Use of Animals in Research.

Laser Treatment

Laser photocoagulation was performed in one eye of each rabbit, the contralateral eye served as a control for the measurements of IOP. Eight 1000 μm Argon laser photocoagulation burns were made at 200 msec and 1000 mW, spaced circumferentially at regular intervals.

IOP Measurement

IOP was recorded with a pneumotonometer (Alcon, Ford Worth, TX) immediately before laser treatment to define baseline values and at various time intervals post-treatment. The change in IOP in the laser-treated and control eyes was calculated by subtracting the baseline IOP from the measured IOP. The corrected change in IOP was then obtained by subtracting the change in IOP in the control eye from that in the treated eye.

Determinations in Aqueous Humor

Paracentesis of the anterior chamber was performed 120 min after laser treatment, using a 27 gauge needle, perforating the cornea in the superior limbal area, removing 0.2 ml of aqueous humor for determinations of protein and prostaglandin E2. Protein was determined with the Bradford method, PGE2 with a radio immunoassay.

Preparation of Drugs

A solution of BN 52021 (Institut Henri Beaufour, Les Plessis-Robinson, France) was prepared immedi-
Fig. 1. The effect of platelet-activating factor (PAF) on the difference in intraocular pressure (IOP) between treated and control eyes in rabbits. The mean corrected ΔIOP, expressed as described in Materials and Methods, is plotted as a function of time after local application of 300 µg (○) and 1000 µg (●) of PAF to one eye. Points represent mean of six rabbits, bars indicate SEM. Analysis by a one-tailed Wilcoxon’s matched-pairs signed-ranks test indicates that a significant (●/● < 0.05) rise in IOP occurred at 15 and 30 min after application of 300 µg of PAF and at 15, 60 and 120 min after application of 1000 µg PAF.

Fig. 2. Effect of argon laser photocoagulation of the iris on the difference in intraocular pressure (IOP) between experimental and control eyes in rabbits without drug treatment (○) and in rabbits treated 5 min before laser photocoagulation with BN 52021 (10 mg/kg) (●) or 15 min before photocoagulation with indomethacin (10 mg/kg) (▲). The mean corrected ΔIOP, expressed as described in Materials and Methods, is plotted as a function of time after laser coagulation. Points represent mean of 12 rabbits, bars indicate SEM. Analysis by student t-test indicates that BN 52021 significantly (**/• < 0.01; * < 0.05) prevented the rise in IOP at various time intervals after laser coagulation.

Indomethacin was dissolved immediately before use in 0.9% NaCl by addition of 0.1 M NaOH to pH 7.4.

Results

Local application of 300 µg and 1000 µg of PAF in 100 µl solution to rabbit eyes caused a dose-dependent significant prolongation of an increase in IOP, which lasted up to 120 min (Fig. 1).

Indomethacin was dissolved immediately before use by dissolving the compound in phosphate-buffered saline (pH 7.4) using 0.1 M NaOH and then neutralizing the solution to pH 7.4 with 0.1 M HCl.

PAF (C-18, Novabiochem, Switzerland) was dissolved in ethanol and then brought to final concentration by dilution in phosphate-buffered saline (pH 7.4). The final concentration for ethanol did not exceed 5%.
The corrected change in IOP after laser treatment shows a hypertensive phase of about 3 hr, followed by a hypotensive interval. Prophylactic intravenous administration, of BN 52021 (10 mg/kg) 5 min before laser treatment, abolishes the hypertensive phase, whereas prophylactic intraperitoneal administration of indomethacin (10 mg/kg), 15 min before laser treatment, has no effect (Fig. 2).

Elevated levels of protein and PGE₂ were measured in the aqueous humor 2 hr after laser irradiation. Prophylactic administration of BN 52021 and of indomethacin shows significantly lower levels of protein and PGE₂ in comparison to those in laser-treated control animals (Table 1).

**Discussion**

The rise in IOP after topical administration of PAF on the normal rabbit eye and the effect of the specific PAF antagonist BN 52021, but not of indomethacin, on the rise in IOP after laser treatment are suggestive for a role of PAF as mediator in this ocular inflammatory response. Although the specific mechanism for these effects remains unclear, elevation of IOP by topical PAF may be accomplished by increase of aqueous inflow through direct stimulation of the active secretory component of aqueous production in the ciliary processes or of the passive component, the ultrafiltrate, by effect on the anterior ocular microcirculation. In addition, microvascular modulation by PAF of aqueous outflow is possible as well.

The partial inhibition of increase in protein by BN 52021 and by indomethacin implicates both PAF and PGE₂ as mediators in the breakdown of the blood–aqueous barrier. In vitro experiments on iris tissue suggest that inflammatory effects of PAF also may proceed indirectly by modulation of the production of prostaglandins.⁶

Although the human eye is much less responsive to laser injury than the rabbit eye,³ there are striking parallels between the clinical situation following laser trabeculoplasty in man and of the laser-induced response of the eye in rabbits. Also, in men inhibitors of cyclooxygenase are without effect on IOP, whereas some effect has been found on flare, a sign of disruption of the blood–aqueous barrier.¹

Therapeutic use of BN compounds in the treatment of elevated IOP after laser treatment seems possible, especially because these compounds are relatively nontoxic and are also effective in oral use.⁷ In other models of ocular inflammation at the surface of the eye BN 52021 was effective after local application.¹⁰

**Key words:** platelet-activating factor, antagonist, rabbit, iris, laser irradiation

**References**


**Table 1. The effect of PAF antagonist BN 52021 and indomethacin on the concentration of protein and PGE₂ in the anterior chamber of the rabbit eye after argon laser coagulation of the iris**

<table>
<thead>
<tr>
<th></th>
<th>Protein (g/l)</th>
<th>PGE₂ (ng/ml)</th>
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<tbody>
<tr>
<td>Controls (n = 12)</td>
<td>10.6 ± 0.9</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>BN 52021 (10 mg/kg) (n = 12)</td>
<td>6.1 ± 0.7*</td>
<td>1.1 ± 0.1*</td>
</tr>
<tr>
<td>Indomethacin (10 mg/kg) (n = 12)</td>
<td>3.4 ± 0.7†</td>
<td>0.10 ± 0.02†</td>
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<tr>
<td>Primary aqueous</td>
<td>0.35 ± 0.05</td>
<td>0.04 ± 0.01</td>
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All values are mean ± SEM. Significance of difference of protein and PGE₂ compared to controls: *P < 0.01; †P < 0.001 (student t-test).