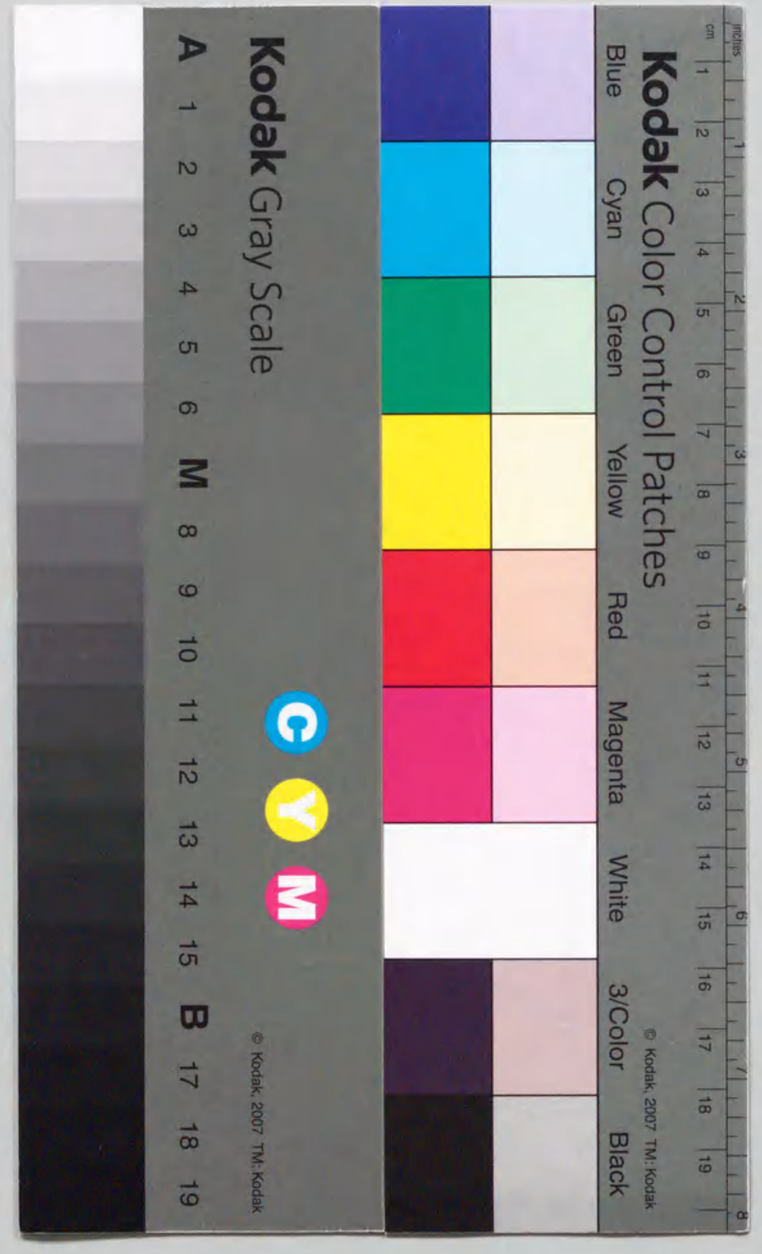

論　文　目　録

岐阜大学

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主論文

Biphasic intraocular pressure response to Q-switched Nd:YAG laser irradiation of the iris and the apparent mediatory role of prostaglandins.
平成2年12月発行　Exp. Eye Res. 51：531～536　1冊

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1）d-チモロール点眼液の正常人眼眼圧などに及ぼす影響について　1冊
昭和61年6月発行　日眼会誌　90(6)：866～870

2）喘息を有する緑内障患者へのβ-遮断剤　1冊
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3）Clonidine点眼によるNd:YAGレーザー虹彩切開術後眼圧上昇の予防　1冊
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4）毛様体冷凍術　1冊
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5）Use of apraclonidine to reduce acute intraocular pressure rise following Q-switched Nd:YAG laser iridotomy　1冊
平成元年1月発行　Ophthalmic Surgery　20(1)：49～52

6）The prevention of an acute rise in intraocular pressure following Q-switched Nd:YAG laser iridotomy with clonidine　1冊
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7）Ocular hypotensive effect of 8-hydroxycarteolol, a metabolite of carteolol　1冊
平成元年1月発行　International Ophthalmology　13：85～89

8）交感神経 α_2-agonist（Clonidine）によるレーザー虹彩切開術後の眼圧上昇抑制効果に関する実験的研究　1冊
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9）Nd:YAGレーザー虹彩照射に対する眼反応と交感神経 α_2-agonistについて　1冊
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主論文

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(2)

Biphasic Intraocular Pressure Response to Q-switched Nd:YAG Laser Irradiation of the Iris and the Apparent Mediatory Role of Prostaglandins

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In rabbits, laser irradiation of the iris causes an immediate rise in intraocular pressure (IOP), with a concomitant increase of prostaglandins (PGs) in the aqueous humor. We studied IOP responses to Q-switched Nd:YAG laser application to the iris in unanesthetized rabbits, and found that a prolonged IOP reduction lasting for 6–24 hr invariably followed the transient IOP rise of 0·5–2 hr duration. The magnitude of both the IOP rise and reduction was dependent on the level of laser energy. A masked, randomized study revealed that the intraperitoneal administration of indomethacin (50 mg kg^{-1}) prior to laser application significantly reduced the ocular hypertensive and hypotensive responses to laser irradiation (energy: 24 mJ). The maximum IOP rise from baseline was $5{\cdot}4 \pm 3{\cdot}0$ mmHg ($n = 10$) with the intraperitoneal vehicle and $1{\cdot}5 \pm 4.2$ mmHg ($n = 10$) with intraperitoneal indomethacin administration. Thus, the difference was statistically significant ($P < 0{\cdot}025$, Student's *t*-test). The maximum IOP reduction from baseline was $-8{\cdot}5 \pm 2{\cdot}6$ mmHg ($n = 10$) with the intraperitoneal vehicle and $-4{\cdot}0 \pm 2{\cdot}4$ mmHg ($n = 10$) with intraperitoneal indomethacin ($P < 0{\cdot}001$, Student's *t*-test).

The concentration of PGE_2 in the aqueous humor, as determined by radioimmunoassay on samples obtained at 2 and 4 hr after laser application, was found to be significantly increased in rabbits that received the vehicle solution but not in animals that were pretreated with intraperitoneal injection of indomethacin. This suggests that this PG or other cyclooxygenase products are involved with mediation of the initial IOP increase and the prolonged decrease in IOP that follows laser irradiation of the iris.

Key words: Nd:YAG laser; iris; intraocular pressure; prostaglandin; PGE_2; aqueous humor; indomethacin; rabbit.

1. Introduction

The response of intraocular pressure (IOP) to Q-switched Nd:YAG laser irradiation to the iris has been studied in animals (Schrems et al., 1983, 1984b; Gailitis et al., 1986; Liu et al., 1988) and humans (Robin and Pollack, 1984; Schrems, Eichelbroenner and Krieglstein, 1984a; Henry et al., 1986; Moster et al., 1986; Schwartz et al., 1986; Shirato et al., 1987; Taniguchi et al., 1987). These studies demonstrated an acute postlaser IOP rise.

However, most of these studies were designed to clarify the IOP changes that occurred within 10 min to 3 hr following the laser irradiation; little is known about the IOP responses over longer periods of time. In our recent study we determined the IOP responses of unanesthetized rabbits to Q-switched Nd:YAG laser application to the iris and found that a prolonged IOP reduction, lasting for 6–24 hr, invariably followed the transient IOP rise of 0·5–2 hr duration (Sugiyama et al., 1989).

The purpose of the present study was to determine in rabbits the possible dose-response relationship between the biphasic IOP response and the energy level of Q-switched Nd:YAG laser application to the iris, and to clarify the mechanisms of this IOP response.

It has been reported that argon or Nd:YAG laser irradiation of the rabbit iris causes an immediate IOP rise, with a concomitant increase in prostaglandins (PGs), particularly PGE_2 and $PGF_{2\alpha}$ in the aqueous humor (Weinreb, Weaver and Mitchell, 1985; Gailitis et al., 1986). Camras and co-workers demonstrated that topical application of PGE_2 to rabbit eyes produced a biphasic IOP response, with an initial transient hypertension followed by a marked hypotension (Camras, Bito and Eakins, 1977). Their report promoted us to examine the possibility that PGs are responsible for the biphasic IOP response after laser treatment. In order to elucidate the possible role of PGs in the IOP changes following laser irradiation of the iris, the effect of indomethacin, a potent cyclooxygenase inhibitor (Ferreria, Moncada and Vane, 1971; Vane, 1971; Jaffe, Podos and Becker, 1973), on IOP and on aqueous humor PGE_2 concentration was studied in our experiments on rabbits.

2. Materials and Methods

We used New Zealand albino rabbits of either sex, weighing 2·0–3·0 kg. In all experiments, a Q-switched Nd:YAG laser apparatus (Topaz, LASAG AG, Thun, Switzerland) was used with a Fankhauser's contact lens (CGI 1·4, LASAG AG, Thun, Switzerland) for

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iridotomy. The irradiation administered was multimodal, with a wavelength of 1064 nm and a pulse duration of 12 nsec. Under local anesthesia (0·4% oxybuprocaine HCl ophthalmic solution, Santen Pharmaceutical, Co. Ltd., Japan), the contact lens was placed over the cornea to focus the laser beam on the iris. Laser foci were placed about 3 mm from the pupil margin. We measured IOP with a calibrated pneumotonometer (Alcon, Inc., Fort Worth, TX) under the same local anesthesia.

In each of four or six rabbits, one eye received Q-switched Nd:YAG laser irradiation and the contralateral eye served as a control. The laser energy was set at 2 mJ (2 mJ × 1 pulse × 1 shot), 16 mJ (8 mJ × 2 pulses × 1 shot), 24 mJ (8 mJ × 3 pulses × 1 shot), 48 mJ (8 mJ × 3 pulses × 2 shots), and 80 mJ (10 mJ × 2 pulses × 4 shots) to determine the effect of laser irradiation on IOP. IOP was measured with a pneumotonometer just prior to laser application and at 0·5, 1, 2, 4, 6 and 24 hr after application.

Indomethacin (50 mg kg^{-1}), a cyclooxygenase inhibitor, or vehicle (10 ml kg^{-1}; 0·05 M phosphate buffer) was administered intraperitoneally in a double-blind, randomized manner. One hour after intraperitoneal administration in each of six to ten rabbits, one eye received Q-switched Nd:YAG laser irradiation (energy: 24 mJ) and the other eye served as a control. IOP was measured with a pneumotonometer just prior to the intraperitoneal administration of either indomethacin or vehicle and the laser application, and then at 0·5, 1, 2, 4, 6, 24, 48 and 72 hr after the laser irradiation.

Paracentesis was performed, with a 27-gauge needle under topical anesthesia on some indomethacin-pretreated and some placebo-injected control rabbits 2 or 4 hr after laser irradiation, to obtain about 100 μl of aqueous humor from each eye. The animals were killed by intravenous injection of a lethal dose of sodium pentobarbital after these samples were obtained. The PGE_2 concentration of all aqueous humor samples were determined by a highly sensitive and specific radioimmunoassay technique (Powell, 1980; Kawano et al., 1987).

The results are presented as mean ±S.D.. The comparison of the measured value with the baseline was made using a paired *t*-test. The values among groups were compared using Student's *t*-test and the Wilcoxon rank sum test. A value of $P < 0·05$ was considered significant.

3. Results

The relationship between laser energy and time-course of IOP changes is shown in Fig. 1. In the lasered eyes, we found a significant IOP rise of 0·5–2 hr duration ($P < 0·05$–$P < 0·001$, paired *t*-test) and a significant IOP reduction compared with baseline value ($P < 0·05$–$P < 0·001$, paired *t*-test) which followed the IOP rise and lasted for as long as 24 hr with some energy levels (Fig. 1).

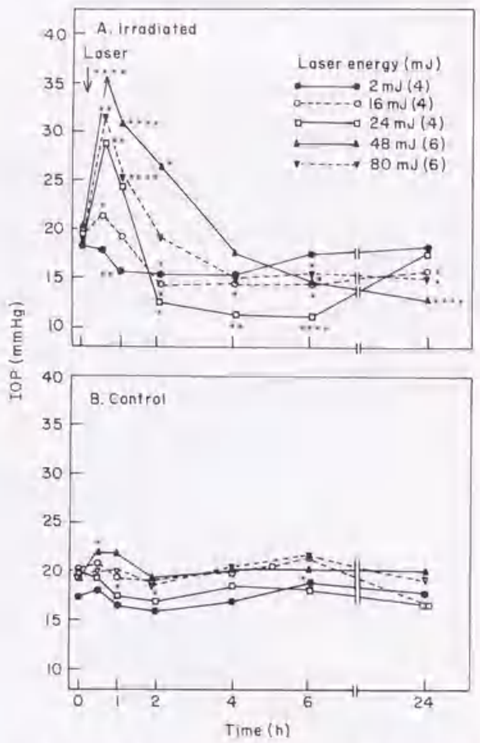

FIG. 1. The time course of IOP changes in rabbit eyes following the irradiation of the iris at different energies (panel A) and in the contralateral control eyes (panel B). Numbers in parentheses indicate the number of eyes irradiated at each energy level. The asterisks next to the means indicate statistically significant IOP changes as compared (paired *t*-test) to the pre-irradiation baseline IOP value: $^{*}P < 0·05$; $^{**}P < 0·01$; $^{***}P < 0·005$; $^{****}P < 0·001$.

The maximum IOP rise, expressed as IOP difference (maximum IOP − baseline IOP) is shown in Table I. With an energy level of 24 mJ or higher, the maximum IOP rise in lasered eyes ranged from 8·9 to 15·4 mmHg, and the difference between the lasered and the control eyes was significant ($P < 0·001$, Student's *t*-test).

The maximum IOP reduction, expressed as the IOP difference (the minimum IOP − the baseline IOP), is also shown in Table I. With all energy levels except for 16 mJ, the amount of the maximum IOP reduction in the lasered eye was significantly larger than that in the untreated eye.

Figure 2(A) shows the maximum IOP rise induced by different energy levels in each lasered eye. The maximum IOP rise was positively correlated with energy levels of 16–80 mJ ($P < 0·001$, $r = 0·7258$). In contrast, in the untreated eyes, there was no correlation between laser energy and maximum IOP rise ($P > 0·10$, $r = 0·0253$).

TABLE I

The relationship between laser energy and the maximum initial increase in IOP during the first hour after irradiation of the iris and the maximum decrease in IOP between 1 and 24 hr after iridial irradiation, as compared to the prelaser baseline IOPs.

		Maximum IOP Rise			Maximum IOP Reduction		
Laser energy (mJ)	Number of eyes	Irradiated eye	Control eye	*P*-value	Irradiated eye	Control eye	*P*-value
2	4	1·6 ± 1·3	2·3 ± 0·5	n.s.	−3·8 ± 1·0	−2·5 ± 0·6	< 0·05
16	4	2·0 ± 1·6	1·5 ± 1·0	n.s.	−6·0 ± 2·2	−4·0 ± 2·6	n.s.
24	4	8·9 ± 3·1	1·1 ± 1·0	< 0·001	−9·9 ± 2·3	−5·0 ± 2·0	< 0·01
48	6	15·4 ± 3·7	3·0 ± 2·7	< 0.001	−8·0 ± 2·5	−2·0 ± 2·6	< 0.005
80	6	12·7 ± 2·4	1·8 ± 1·8	< 0·001	−6·6 ± 1·6	−2·5 ± 3·2	< 0·01

The mean are the maximum IOP values after laser irradiation minus baseline IOP and the minimum IOP values after laser irradiation minus baseline IOP ± S.D. The results are presented as mean ± S.D. The *P* values were calculated according to Student's *t*-test.

The IOP response over time after Nd:YAG laser application (laser energy: 24 mJ) to the iris is shown in Fig. 3. Indomethacin or placebo was administered intraperitoneally 1 hr before the laser treatment. In the placebo-treated group, the laser treatment produced a biphasic response, with a significant initial hypertension ($P < 0·001$, Student's *t*-test) followed by a significant hypotension ($P < 0·001$, Student's *t*-test), as compared with the contralateral untreated eyes [Fig. 3(A)]. In contrast, in the indomethacin-treated group there was no significant difference in IOP between the lasered eye and the contralateral untreated eye, except at 24 hr [Fig. 3(B)].

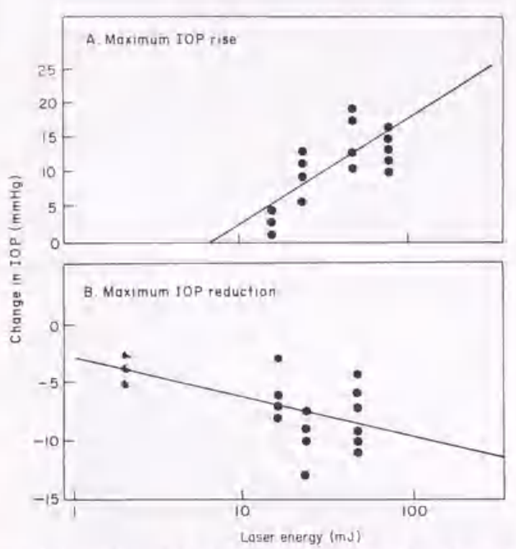

FIG. 2. A, Laser energy and maximum IOP rise (lasered eyes). Maximum IOP rise = maximum postlaser IOP − pre IOP. $Y = 15·1 \times - 13.4$, $r = 0·7258$, $P < 0·001$. B, Laser energy and maximum IOP reduction (lasered eyes). Maximum IOP reduction = minimum postlaser IOP − pre IOP. $Y = -3·5 \times 2·8$, $r = -0·6213$, $P < 0·005$.

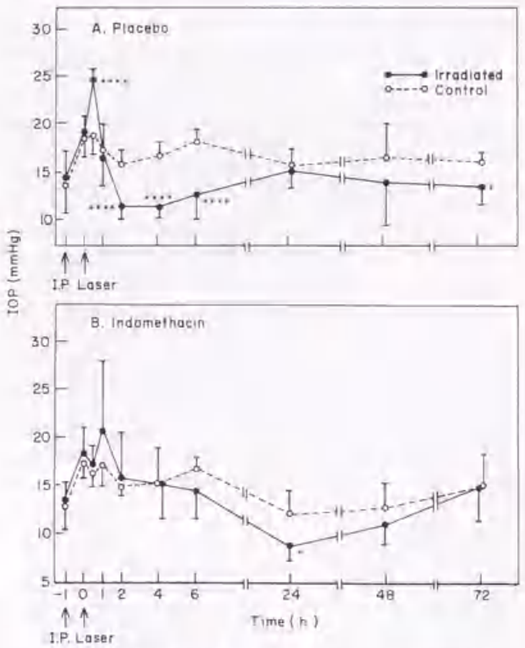

FIG. 3. Postlaser IOP changes pretreated with placebo or indomethacin. I.P. indicates the time of intraperitoneal injection. Laser denotes the time of laser irradiation (24 mJ). The results are presented as mean ± S.D. Six rabbits were used in this experiment. The asterisks next to the means indicate statistically significant IOP changes as compared (paired *t*-test) to the baseline IOP value: $^{*}P < 0·05$, $^{****}P < 0·001$.

TABLE II

Maximum IOP rise and reduction following laser irradiation within 4 hr

	Maximum IOP rise (mmHg)			Maximum IOP reduction (mmHg)		
Pretreatment	Irradiated eye	Control eye	*P*-value	Irradiated eye	Control eye	*P*-value
Placebo ($n = 10$)	$5{\cdot}4 \pm 3{\cdot}0$	$0{\cdot}5 \pm 1{\cdot}8$	$< 0{\cdot}001$	$-8{\cdot}5 \pm 2{\cdot}6$	$-3{\cdot}0 \pm 2{\cdot}1$	$< 0{\cdot}001$
Indomethacin ($n = 10$)	$1{\cdot}5 \pm 4{\cdot}2$	$1{\cdot}3 \pm 2{\cdot}1$	N.S.	$-4{\cdot}0 \pm 2{\cdot}4$	$-2{\cdot}8 \pm 2{\cdot}7$	N.S.
P-value	$< 0{\cdot}001$	N.S.		$< 0{\cdot}025$	N.S.	

Maximum IOP rise = Maximum Postlaser IOP − PreIOP
Maximum IOP reduction = Minimum Postlaser IOP − PreIOP
Mean ± s.d. Statistics: Student's *t*-test

TABLE III

The concentration of PGE_2 in aqueous humor following Nd:YAG laser irradiation of the iris

Time (hr)	Pretreatment	Irradiated eye	Control eye	*P*-value
2	Placebo	$2450{\cdot}0 \pm 1255{\cdot}7$	$25{\cdot}3 \pm 13{\cdot}1$	0·05
	Indomethacin	$42{\cdot}3 \pm 30{\cdot}3$	$18{\cdot}5 \pm 7{\cdot}0$	N.S.
4	Placebo	$1240{\cdot}0 \pm 1074{\cdot}4$	$29{\cdot}5 \pm 9{\cdot}7$	0·05
	Indomethacin	$25{\cdot}8 \pm 6{\cdot}0$	$24{\cdot}2 \pm 22{\cdot}5$	N.S.

Mean ± s.d.; $n = 4$. Statistics: Wilcoxon rank sum test.

The maximum IOP rise and the maximum IOP reduction within 4 hr after the laser treatment are shown in Table II. In the lasered eyes, both the maximum IOP rise and the maximum IOP reduction were significantly suppressed by the indomethacin pretreatment as compared with those treated with placebo ($P < 0{\cdot}025$, $P < 0{\cdot}001$, Student's *t*-test). On the other hand, in the contralateral untreated eyes no significant difference was noted in both the maximum IOP rise and the maximum IOP reduction, regardless of the type of pretreatment.

Aqueous PGE_2 concentrations at 2 and 4 hr after laser treatment (energy: 24 mJ) are listed in Table III. In the placebo-treated group, a marked elevation of aqueous PGE_2 concentration was noted in the lasered eyes. On the other hand, in the indomethacin-treated group no significant change in aqueous PGE_2 content was observed in the lasered eyes.

4. Discussion

Present study demonstrates that application of Q-switched Nd:YAG laser to the iris of rabbits elicited a biphasic IOP response, with both the transient increase in IOP and the subsequent sustained ocular hypotension, clearly depending on the level of laser energy.

That aqueous humor PGE_2 concentration in the lasered eyes was greatly elevated and that indomethacin pretreatment blocked this effect and partially suppressed the observed IOP changes, suggest that this PG, or other cyclooxygenase products, are involved, at least to some extent, in the laser-induced IOP changes in this species.

Substantial evidence was already been presented, suggesting that the initial rise in IOP induced by the laser treatment is mediated by intraocular PG release, presumably related to a breakdown of the blood-aqueous barrier (Unger, Perkins and Bass, 1974; Unger, Cole and Bass, 1977; Schrems et al., 1983; Sanders et al., 1983; Weinreb et al., 1985; Gailities et al., 1986; Liu et al., 1988). Since indomethacin is known to inhibit the synthesis of all cyclooxygenase products to the same extent rather than specific blockade of PGE_2 synthesis (Ferreria et al., 1971; Vane, 1971), we must not conclude that PGE_2 itself is the mediator of the indomethacin sensitive IOP component. Moreover, we have found that indomethacin pretreatment was unable to completely suppress the IOP rise after the laser treatment, even though it significantly inhibited the rise in PGE_2 concentration in the aqueous humor. Thus, we must consider the possibility that cyclooxygenase products are not the sole factors responsible for the IOP elevation, and it is most likely that other factors, such as neurogenic mediation (Unger, 1989), accumulation of tissue debris, or fibrin (Tawara and Inomata, 1987) and neuropeptides (Stjernschantz, Sears and Stjernschantz, 1981; Katayama et al., 1986; Stjernschantz et al., 1986) may also be involved.

It is well known now that increased synthesis of a given PG reflects the increased synthesis of not only

the particular PG that was measured, but all cyclooxygenase products (Kulkarni and Srinivasan, 1989). Thus, we cannot conclude that, the IOP effects we observed in the indomethacin-pretreated rabbit were caused by the intraocular accumulation of PGE_2, as it may very well have been mediated by simultaneously produced $PGF_{2\alpha}$ or other cyclooxygenase products. It is also possible that the initial hypertensive phase is mediated by one PG, such as PGE_2, that has been shown to cause a particularly large initial IOP increase in rabbits (Camras et al., 1977), that seem to be associated with the breakdown of the blood–aqueous barrier. On the other hand, the subsequent prolonged IOP reduction may also be mediated by the more stable $PGF_{2\alpha}$, in addition to PGE_2, which has been shown to be a potent ocular hypotensive agent in all species studied, including rabbits (Bito et al., 1989).

Furthermore, it must be remembered that increased synthesis of PGs is not due to, or at least not primarily due to, stimulation of the cyclooxygenase pathway, but rather it reflects increased release of arachidonic acid (AA) from membrane phospholipid stores (Kulkarni and Srinivasan, 1989). Thus, our observation of a several hundred fold increase in the concentration of PGE_2 in the aqueous humor following laser irradiation of the rabbit iris implies a large increase in AA release, as compared to the normal baseline release of this eicosanoid precursor. This, in turn, implies that the portion of the IOP decrease that was not blocked by indomethacin may well be mediated by other eicosanoids, such as leukotrienes, that are formed from AA via metabolic pathways other than the cyclooxygenase enzyme system.

Thus, even though we cannot rule out the possible contribution of unrelated autacoids, it is clear that laser irradiation of the iris causes a greatly increased AA release. Hence it is most likely to cause an increase in the production of a whole spectrum of eicosanoids, besides PGs. Thus, non-prostaglandin arachidonic acid derivatives may also play a role in the observed IOP responses, and may account for the indomethacin-insensitive portion of the initial IOP increase, the subsequent IOP decrease, or both.

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