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INHIBITORS OF THE ARACHIDONIC ACID CASCADE IN THE MANAGEMENT OF OCULAR INFLAMMATION

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The cardinal signs of ocular inflammation are hyperemia, increased vascular permeability, edema, and infiltration of cells (leukocytes, mast cells, platelets, etc.) into ocular fluids and tissues. In experimental acute anterior uveitis, miosis and a rise in intraocular pressure (IOP) are also seen. Increased IOP during this type of acute inflammation is usually associated with breakdown of the blood- aqueous barrier and the release of proteins and subsequently inflammatory cells into the aqueous humor. In contrast, increased IOP is not typically associated with chronic uveitis. Experimental paracentesis is accompanied by an irritative response characterized by iridial hyperemia, protein exudation into the aqueous humor, and a rebound elevation of IOP, but not by cellular infiltration into the aqueous humor. This irritative response to paracentesis usually disappears within 2 to 3 hours (Eakins, 1976, 1977). Thus, interpretation of reports on the ocular effects of anti-inflammatory drugs is greatly complicated by the fact that they are studied on a variety of different models of ocular inflammation.

The relevance of some of these experimental models to the ocular inflammatory conditions seen in clinical practice, especially to chronic uveitis, remains to be established. Furthermore, the use of the rabbit as an experimental animal and especially the use of the paracentesis response, is of special concern with regard to studies involving the arachidonic acid (AA) cascade since this species was shown to exhibit more exaggerated responses to paracentesis and, indeed, to other forms of ocular irritation than other experimental animals including primates. It should also be noted that prostaglandins (PG.) or other members of the AA cascade appear to play a greater role in this irritative response of the rabbit eye than in the eyes of

other species (Bito, 1984a). In spite of the apparently greater sensitivity of the rabbit eye to some effects of PGs it seems that even in this species, PGs may play only a modulatory role enhancing or altering the effects of other mediators of the ocular irritative and inflammatory responses. Some current concepts with regard to such mediatory and modulatory roles are reviewed in other chapters of this volume (Unger, 1989; Bhattacherjee, 1989). In this chapter, we will review aspects of the AA cascade relevant to ocular inflammation and use of steroidal and nonsteroidal anti-inflammatory agents in relation to the inhibition of this cascade.

THE ARACHIDONIC ACID (AA) CASCADE

The polyunsaturated fatty acid, AA, (C20:4) is converted into PGs, thromboxane, and a variety of other eicosanoids in ocular tissues (see Kulkarni and Srinivasan, 1989; Bhattacherjee, 1989; Bazan H, 1989; Bazan N, 1989). Since PGs are not stored (Änggård et al., 1971) but are taken up by active transport (Bito, 1975; Bito et al., 1976) and are inactivated by PG dehydrogenase (Änggård et al., 1971) in most tissues except possibly the eye (Eakins et al., 1974; Bito, 1975), the biological activities of these autacoids depend on release of the substrate AA from the phospholipid pool. Once AA is released by mechanical stimuli such as trauma, injury, or massage (Ferreira et al., 1974), or by chemical stimuli – for example: bradykinin (Willis, 1969), histamine (Juan and Samez, 1980), or catecholamines (Willis, 1969; Ferreira et al., 1973), it is quickly converted into biologically active compounds of PGE_2, PGD_2, and $PGF_{2\alpha}$, and unstable compounds such as thromboxane A_2 (Hamberg et al., 1974) and PGI_2 (Bunting et al., 1976a, 1976b) by the cyclooxygenase enzyme system. AA is also converted into various lipoxygenase products by different lipoxygenases (Samuelsson, 1980; see also Bhattacherjee, 1989).

Among the products formed by the lipoxygenase pathways, leukotriene B_4 is a potent chemotactic and chemokinetic agent for leukocytes (Palmer et al., 1980; Samuelsson, 1981), whereas leukotriene C_4 and D_4 represent the slow reacting substances of guinea pig anaphylaxis (Samuelsson, 1980, 1981). Leukotriene C_4 and D_4 are mediators of allergic and asthmatic reactions (Samuelsson, 1981). They are also thought to cause vasoconstriction *in vivo* (Burke et al., 1982), to release thromboxanes from platelets (Engineer et al., 1978), and to increase vascular permeability (Palmer et al., 1980; Samuelsson, 1981; Burke et al., 1982). AA is also converted into other chemotactic hydroxy acids by various lipoxygenases. The reader is referred to other chapters in this volume for more detailed accounts of the synthesis of various eicosanoids by the retina (Bazan N, 1989), cornea and lens (Bazan H, 1989), by the anterior uvea and conjunctiva (Kulkarni and Srinivasan, 1989), and the release of these autacoids into intraocular compartments *in vivo* (Bhattacherjee, 1989).

AA METABOLITES IN OCULAR INFLAMMATION

Ambache and co-workers extracted from the rabbit iris an ether-soluble substance that had the capacity to stimulate smooth muscle. This substance, named "irin," was later found to contain a mixture of E and F PGs (Ambache and Brummer, 1968). Since these early studies were done, further experimental evidence (Eakins 1976, 1977; Bhattacherjee, 1980; Kulkarni and Srinivasan, 1983a; Sears, 1984) has been presented to suggest that AA metabolites play an important role in certain forms of ocular inflammation. Specifically, it has been observed that (1) ocular tissues of different species, including humans, are capable of synthesizing cyclooxygenase and lipoxygenase products from AA; (2) increased levels of cyclooxygenase and lipoxygenase products are present in the aqueous humor of inflamed eyes of both experimental animals and humans; (3) inhibitors of AA metabolism prevent or significantly reduce certain types of ocular inflammation; (4) cyclooxygenase and lipoxygenase products can reproduce one or more of the characteristic signs of ocular inflammation when applied topically, intravitreally, or intracamerally (see Eakins, 1977).

SYNTHESIS OF CYCLOOXYGENASE AND LIPOXYGENASE PRODUCTS FROM AA BY OCULAR TISSUES

In experiments using radioactively labeled AA, it has been shown that some rabbit, bovine and human ocular tissues, specifically the conjunctiva, iris and retina can incorporate AA into their membrane phospholipid pool (Culp et al., 1970a, b; Abdel-Latif and Smith, 1982; Birkle and Bazan, 1984; Bazan and Reddy, 1985; PS Kulkarni and AA Abdel-Latif, unpublished observations). The rabbit iris, for example, incorporates AA into its glycerolipids and about 65% of the total radioactivity derived from labeled AA is recovered in triacylglycerol, 20% in phosphatidylcholine, 6% in diacylglycerol, 5% in phosphatidylethanolamine, and 3% in phosphatidylinositol (Abdel-Latif and Smith, 1982). In the human iris, AA has been found in phosphatidylethanolamine and phosphatidylcholine (Culp et al., 1970a). Recently, we have further characterized the phospholipid composition of the human anterior uvea and demonstrated an abundant distribution of phosphatidyl choline, phosphatidyl ethanolamine, and triglycerides in the phospholipid membrane of this tissue. These studies indicated that the human anterior uvea is a rich source of AA.

Ocular tissues such as the cornea, conjunctiva, anterior uvea (iris-ciliary body), and retina synthesize cyclooxygenase and lipoxygenase products from AA (Kulkarni and Srinivasan, 1983a; Bazan and Reddy, 1985). All species studied such as the rabbit, ferret, dog, cat, cow, and cynomolgus and rhesus monkeys, as well as humans, convert AA in their conjunctiva and anterior uvea into many types of PGs and thromboxanes. Among these tissues, the bovine and human anterior uvea had

comparatively little cyclooxygenase activity (Kulkarni and Srinivasan, 1989). However, these tissues synthesize cyclooxygenase products from PGH_2 (Kulkarni et al., 1977; Kulkarni, 1981). The conjunctiva and iris-ciliary body of dogs, cats, pigmented and albino rabbits, monkeys and humans also use AA to synthesize the lipoxygenase products 12-HETE, 5-lipoxygenase products, and LTB_4 which are known to be chemotactic for polymorphonuclear leukocytes (Kulkarni and Srinivasan, 1983b, 1984a; Bhattacherjee and Eakins, 1984) and slow reacting substance (SRS), a mixture of LTC_4, LTD_4 and LTE_4 (Kulkarni and Srinivasan, 1989).

The results are inconclusive regarding PG synthesis in the mammalian lens. Van Dorp et al. (1967) and Belisle et al. (1982) have presented evidence suggesting that the pig and rat lens have a low but measurable PG synthetic capacity. However, other investigators (Kass and Halinberg, 1979; Guivernau et al., 1982; Taylor et al., 1982; Fu, 1983) have been unable to detect PG production in the rabbit or calf lens. This discrepancy may result from the use of different techniques to measure PGs in different species. More current information on this subject is presented elsewhere in this volume (Bazan H, 1989).

LEVELS OF CYCLOOXYGENASE AND LIPOXYGENASE PRODUCTS IN THE AQUEOUS HUMOR OF IRRITATED AND INFLAMED EYES

We have recently observed the release of LTB_4 (Kulkarni et al., 1986) and LTC_4 (unpublished observations) into the aqueous humor following paracentesis, as well as after the intravitreal injection of endotoxin into rabbits eyes. PGs are released into the aqueous humor during immunological ocular inflammation produced by injecting bovine serum albumin into the vitreous of the rabbit (Eakins et al., 1972). This type of experimental uveitis results in the invasion of the anterior chamber by inflammatory cells. The level of PGs in the aqueous of inflamed rabbit eyes was about 40 to 100 times higher than in the aqueous of control eyes (Eakins et al., 1972). Bhattacherjee (1975) also demonstrated PG release during uveitis induced by the injection of Shigella endotoxin into the vitreous. A substantial amount of PG-like activity has been found in the aqueous humor of patients with acute uveitis, glaucomatocyclitic crises, and Bechet's disease (Eakins, 1976). Little or no activity has been found in the aqueous of control patients with cataracts or with uveitis who have been treated with topical steroids (Eakins, 1976).

Unlike other tissues (lung, kidney, etc.), ocular tissue such as the rabbit anterior uvea have little or no ability to inactivate PGs, i.e., they lack PG dehydrogenase (Eakins, 1976). Furthermore, when experimental anterior uveitis is induced in rabbits, PGs released during inflammation are no longer removed by an active transport process from the intraocular fluids by the anterior uvea (Bito, 1973). Thus, PGs accumulate in the aqueous humor. The PG-like activity had been associated with PGs of the E type (Eakins, 1976, 1977). However, these studies have been

performed only in rabbits. It is not yet known whether the elevation of PGs in the human aqueous in association with acute uveitis is caused by failure of the PG transport mechanism in the anterior uvea, by an increased production of PGs by inflamed anterior uveal tissue, or by polymorphonuclear cells (PMNs) or a combination of these processes.

In external ocular inflammation such as that produced by corneal epithelial denudation, PGE_2 and LTB_4 are released into the rabbit tear fluid (Kulkarni and Srinivasan, 1983a; Kulkarni et al., 1986). In addition, the presence of LTB_4 in human tears has recently been demonstrated in allergic conjunctivitis (Bisggard et al., 1984).

ALLEVIATION OF EXPERIMENTAL OCULAR INFLAMMATION BY INHIBITORS OF AA METABOLISM

Indomethacin and aspirin are two nonsteroidal anti-inflammatory drugs that have been most frequently used in experimental ocular inflammation (Flower, 1974; Vane, 1976). It has been found that in the endotoxin and BSA-induced uveitis models, administration of indomethacin inhibits some signs of intraocular inflammation, such as the iridial hyperemia and the increase of protein concentration in the aqueous resulting from breakdown of the blood-aqueous barrier in rabbits (Kulkarni et al., 1981). In this study, indomethacin also inhibited the increase in PG concentration in the aqueous humor of rabbits.

Paradoxically, topical administration of indomethacin in the BSA-induced uveitis model in rabbit potentiated the accumulation of PMNs into the aqueous (Kulkarni et al., 1981). Higgs et al. (1979) have also demonstrated that in the rat low doses of indomethacin potentiate the local accumulation of PMNs induced by intraperitoneal carageenan, whereas high doses inhibited this response. Because low doses of indomethacin inhibit the cyclooxygenase but not the lipoxygenase pathways, these authors suggested that the potentiation of chemotaxis by indomethacin was caused by enhancement of chemotactic lipoxygenase product formation. To support this hypothesis, these authors demonstrated that the chemotactic response was completely inhibited by BW755, an inhibitor of both cyclooxygenase and lipoxygenase enzymes (Higgs et al., 1979).

In the rabbit corneal epithelial denudation model, we compared the effects of nonsteroidal agents on PMN accumulation in the tear fluid, on wound healing, and on the synthesis of cyclooxygenase and lipoxygenase products (Srinivasan, 1982; Kulkarni and Srinivasan, 1984b, 1985). Intraperitoneal administration of high doses of cyclooxygenase inhibitors (indomethacin, aspirin, flurbiprofen or ketoprofen) inhibited the release of PMNs into the tear fluid. However, low doses of indomethacin and aspirin, but not flurbiprofen or ketoprofen, potentiated the release of PMNs into the tear fluid. Furthermore, we observed that intraperitoneal admin-

istration of doses of indomethacin that potentiated the PMN response inhibited cyclooxygenase activity in the rabbit conjunctiva substantially but not completely, and without affecting lipoxygenase activity (synthesis of 12-HETE, 5-HETE or 5,12 di-HETE from ^{14}C-AA). Nonsteroidal drugs (indomethacin, aspirin, flurbiprofen, ketoprofen, and enolicam), when applied topically, also significantly inhibited both the PMN response and cyclooxygenase activity in the rabbit conjunctiva in a dose-dependent fashion. Flurbiprofen, ketoprofen, and enolicam were equally effective in inhibiting the PMN response and PG synthesis, and were more potent in this regard than indomethacin or aspirin.

Pretreatment with indomethacin or imidazole also prevented the sustained rise in IOP that occurs after experimental corneal burns (Paterson et al., 1978) or after topical application of PGE (Zink et al., 1975a) or nitrogen mustard (Zink et al., 1975b). Because imidazole is a specific thromboxane-synthetase inhibitor (Moncada et al., 1977), it is possible that thromboxane, a potent vasoconstrictor, may elevate IOP in rabbits.

PRODUCTION OF CHARACTERISTIC SIGNS OF OCULAR INFLAMMATION BY EICOSANOIDS

Intracameral administration of PGs of the E and F type and their precursor, AA, produce modest to severe miosis in rabbits and a sustained rise in IOP that is closely associated with large increases in the protein concentration of the aqueous humor and with iridial hyperemia (Ambache and Brummer, 1968; Eakins 1976, 1977; Bhattacherjee, 1980; Kulkarni and Srinivasan, 1983a). Camras et al. (1977) observed a biphasic IOP response following topical application of high PG doses to the rabbit eye; i.e., an initial rise in IOP followed 3 to 4 hours later by prolonged hypotension without miosis, whereas low doses of $PGF_{2\alpha}$ caused only ocular hypotension. In other species including monkeys and cats, intracameral injection of sufficient doses of PGs E_1 E_2, $F_{1\alpha}$ and $F_{2\alpha}$ increased the IOP and the protein content of the aqueous (Eakins, 1976). However, Bito and co-workers have recently demonstrated that topical application of $PGF_{2\alpha}$ decreases IOP without causing significant flare in cats and monkeys (Stern and Bito, 1982; Bito et al., 1983). Although $PGF_{2\alpha}$ was found to be a potent miotic in cats, but not in primates, ocular hypotensive doses of PGE_2 or PGs of the A and B type do not cause significant miosis in either cats or primates (Miranda and Bito, 1989). Studies on the ocular hypotensive effects of topically applied PGs in experimental animals and in humans are described in detail elsewhere in this volume (Alm and Villumsen, 1989; Bito et al., 1989).

The ocular effects of some of the other, more recently discovered, eicosanoids, including PGI_2, 6-keto-$PGF_{1\alpha}$ and 6-keto-PGE_1, as well as analogues of PGH_2 and PGE_2, have been assessed in rabbits (Kulkarni and Srinivasan, 1982). In these

studies, intravitreal or topical administration of PGI_2, 6-keto-PGE_1 or PGE_2 increased IOP. High doses of PGE_2 increased but low doses decreased the IOP. Interestingly, two PG receptor antagonists, polyphloretin phosphate which was administered by close-arterial infusion and by intravitreal or subconjunctival routes (Eakins, 1976), and N-0164, which was administered intravitreally, (Kulkarni and Srinivasan, 1982) antagonized ocular hypertension but not the hypotensive effect of intracamerally or topically administered PGE_2. This suggests the presence of at least two types of PG receptors, one mediating the ocular hypertensive response and the other mediating the hypotensive response. Additionally, polyphloretin phosphate and N-0164 also inhibited the breakdown of the blood-aqueous barrier response induced by topically, intracamerally, or intravitreally administered PGs (Eakins, 1976; Kulkarni and Srinivasan, 1982). When some PGs, such as PGD_2 were administered either topically or intravitreally, they had little effect on the IOP but increased the protein content of the aqueous, whereas PGI_2 administered in similar ways had only a small effect on the aqueous protein content but significantly increased IOP (Kulkarni and Srinivasan, 1982). These results suggest that some of the inflammatory signs of ocular inflammation are not necessarily interdependent or sequential and can be studied separately by using appropriate drugs.

In a study of external ocular inflammation, topical application of low doses of PGE_1, PGE_2, or PGI_2 to the uninjured eye caused the release of PMNs into the tear fluid of rabbits (Srinivasan and Kulkarni, 1980) but higher doses had no effect. Other PGs, such as $PGF_{2\alpha}$ had no effect on leukocyte release in the tear fluid. Topical PGs E_2, E_1, and I_2 which affected chemotaxis or chemokinesis, also caused some conjunctival vasodilation. In addition, thromboxane A_2 (half life, 30 sec) produced by incubating rabbit platelets with AA had no significant effect on PMN chemotaxis but caused significant iridial and conjunctival hyperemia.

The recent discovery of leukotrienes (Samuelsson, 1980) has stimulated great interest in their role in inflammation. LTB_4 has been identified as the most chemotactically potent of all leukotrienes tested in the rat model of carageenan-induced inflammation (Palmer et al, 1980; Bhattacherjee and Eakins, 1984). Recently, Bhattacherjee and Eakins (1984) demonstrated that intracamerally administered LTB_4 is also the most potent of all lipoxygenase and cyclooxygenase products and chemotactic polypeptide (FMLP) tested with respect to the induction of chemotaxis in the rat anterior chamber. In their study, these authors found that intracameral PGE_2 had no effect on the PMN response. In preliminary experiments, we also observed that intracameral injection of LTB_4 released a substantial number of PMNs into the aqueous of owl monkey eyes (PS Kulkarni, J Denlinger, EA Balazs, BD Srinivasan, unpublished observations).

We have also demonstrated that both prednisolone acetate and indomethacin inhibit the neovascularization of the rabbit cornea that usually occurs after

complete corneal epithelial denudation; prednisolone acetate being a more potent inhibitor than indomethacin (Srinivasan, 1982). Flurbiprofen was also reported to inhibit neovascularization in radially keratotomized or chemically injured rabbit eyes (Cooper et al., 1980; Katz et al., 1984).

OTHER PROPERTIES OF NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

Although it has been demonstrated that the well known anti-inflammatory drugs, such as indomethacin and aspirin, are potent inhibitors of the cyclooxygenase pathway, they also have other properties that may contribute to their anti-inflammatory effects. For example, in high doses, both drugs may inhibit lipoxygenase activity (Bragt and Bonta, 1980; Sirois et al., 1984). At low concentrations, indomethacin inhibits phospholipase A_2 of rabbit PMNs but not that found in the venom of the Russell viper and bee or in the pig pancreas (Kaplan et al., 1978). Additionally, indomethacin inhibits phosphodiesterase activity (Flores and Sharp, 1972), whereas imidazole (a thromboxane synthetase inhibitor), which can prevent a sustained rise in IOP subsequent to experimental corneal burns, is a phosphodiesterase activator (Butcher and Sutherland, 1962).

It has also been shown that indomethacin is a competitive inhibitor of the binding site of the chemotactic peptide FMLP to human PMNs (Abita, 1981). Furthermore, flurbiprofen, ibuprofen, indomethacin, ketoprofen, and benoxiprofen inhibit FMLP-elicited release of granule-associated enzymes from human neutrophils (Smith and Iden, 1980). Other studies have indicated that nonsteroidal drugs inhibit PMN locomotion and chemotaxis, probably by a direct effect on the PMNs (Smith and Iden, 1980; Abita, 1981; Perianin et al., 1985). It is noteworthy that these nonsteroidal anti-inflammatory drugs have, in at least some experimental models of inflammation, the paradoxical effect of potentiating the effects of the inflammatory response (Kulkarni et al., 1981). Recently, a preliminary study demonstrated that acetyl salicylate (aspirin), salicylate, but not sodium salicylate, inhibits lens protein aggregation *in vitro* by trapping (electron) oxygen radicals produced by arachidonate or linolinate hydroperoxidation (E Cottlier, personal communication). Other nonsteroidal drugs besides aspirin such as ibuprofen and acetamenophen were also found to be anti-cataract agents and the mechanism of their anti-catract action is not mediated by intervention with AA metabolism (Harding and Heyningen, 1988). Therefore, all reported actions of indomethacin and similar compounds are not necessarily mediated by inhibition of AA metabolism.

CLINICAL USES OF STEROIDAL AND NONSTEROIDAL AGENTS IN OCULAR INFLAMMATION

Corticosteroids such as prednisolone acetate, flurometholone, and dexamethasone are currently in clinical use as anti-inflammatory agents. Although, corticosteroids are used in the treatment of various ocular inflammatory diseases, their

long term use is severely limited by such side effects as ocular hypertension, cataracts, immunosuppression and increased susceptibility to herpes infections. Thus, there is an obvious need to develop steroidal type of anti-inflammatory drugs or non steroidal compounds that have a steroid-like effect but do not share with currently used steroids their ocular side-effects.

One mechanism of the anti-inflammatory action of corticosteroids is thought to be the induction of synthesis of a specific protein(s) that inhibit(s) phospholipase A_2, an enzyme responsible for the release of AA (Blackwell et al., 1980; Hirata et al., 1980). Thus, at least some of the anti-inflammatory effects of such steroids are thought to be due to their inhibitory effects on the production of prostaglandins as well as other eicosanoids produced through both the cyclooxygenase and lipoxygenase pathways. Because nonsteroidal anti-inflammatory agents, such as indomethacin, interfere with AA metabolism through the cyclooxygenase pathway, and were shown to inhibit at least some aspects of experimental ocular inflammation in rabbits, clinical research into their therapeutic uses is now underway (see Camras and Miranda, 1989).

THE EFFECTS OF CYCLOOXYGENASE INHIBITORS ON SURGICAL MIOSIS

The prevention of pupillary constriction during intraocular surgery is an important goal, and it has been suggested that the topical or systemic use of indomethacin can successfully prevent pupillary constriction during intraocular surgery (Sawa and Masuda, 1976; Jaffe, 1981). For example, indomethacin and flurbiprofen were found to prevent miosis following surgical trauma that occurs during cataract extraction. It must be noted however, that in spite of initial reports, more recent studies indicate that while some PGs do have some miotic effect in some species, such as $PGF_{2\alpha}$ in cats, PGs in general cannot be regarded as effective miotic agents, (see Bito, 1984b; Bito et al., 1987; Miranda and Bito, 1989). In fact, physiologically significant dose-dependent PG-induced miosis has not been reported in normal primate eyes (see Miranda and Bito, 1989) and doses of $PGF_{2\alpha}$, its salt or ester sufficient to yield significant IOP reduction were found to have no miotic effects in humans (Camras et al., 1988; Alm and Villumsen, 1989). Flurbiprofen has recently been approved by the FDA for topical use in reducing pupillary constriction during cataract surgery (Keates and McGowan, 1984). The mechanism of this claimed anti-miotic effect has not been elucidated. Topical indomethacin has also been used to prevent postoperative inflammation following cataract extraction (Mishima et al., 1989). The putative role of PGs in miosis associated with intraocular surgery is discussed in detailed elsewhere in this volume (Camras and Miranda, 1989).

THE EFFECTS OF NONSTEROIDAL ANTI-INFLAMMATORY AGENTS ON THE BLOOD-AQUEOUS BARRIER (BAB)

Neufeld et al. (1972) reported that systemic administration of aspirin minimizes the paracentesis induced breakdown of the BAB in rabbits, as revealed by a reduction of the protein concentration in the secondary aqueous. However, such BAB breakdown induced by some other means was not effectively minimized by this nonsteroidal anti-inflammatory agent. Furthermore, Kass et al. (1975) could not demonstrate a protective effect of either aspirin or indomethacin against paracentesis-induced increase in aqueous humor protein concentration in rhesus monkeys.

While further studies are clearly required to substantiate or explain this striking apparent species difference, the study by Neufeld et al. (1972) tended to indicate that even in rabbits only some forms of ocular irritative response and associated BAB breakdown are mediated by PGs – or possibly other cyclooxygenase products, such as prostacyclin or thromboxane. Indeed, more recent studies suggest that PGs are modulators rather than mediators of the ocular irritative response in rabbits (see Unger, 1989). Furthermore, the report by Kass et al. (1975) on the lack of effect of aspirin and indomethacin on the monkey eye raises fundamental questions with respect to the role of PGs in the ocular responses to trauma in primates. Nonetheless, based on initial observations on rabbits, the concept that such nonsteroidal anti-inflammatory drugs protect the BAB led to their use in clinical ophthalmology. Mochizuki et al. (1977) reported that 0.5% indomethacin in sesame oil vehicle reduced the incidence of anterior chamber cellular reaction and aqueous flare following cataract surgery. Sander and Kraff (1984) also found that topical treatment with 1% indomethacin reduced leakage of fluorescein into the anterior chamber (breakdown of blood-aqueous barrier) after extracapsular cataract extraction and intraocular lens implantation. Interestingly, they also reported that the use of combined treatment with steroidal and nonsteroidal anti-inflammatory drugs such as indomethacin and dexamethasone resulted in less fluorescein leakage during the second postoperative week than did the use of dexamethasone alone. This clearly suggests that the involvement of the AA cascade in the protection of the BAB is a complex phenomenon and that steroidal and nonsteroidal anti-inflammatory agents may enhance BAB stability by a variety of means, not all of which is necessarily related to inhibition of the AA cascade.

Research has been undertaken recently to assess the effectiveness of Ketorolac, a new nonsteroidal anti-inflammatory agent, in the prevention of postsurgical breakdown of the blood-aqueous barrier (Flach et al., 1987, 1988). In one such study, Flach et al. (1988) found that topical administration of ketorolac tromethamine before and after extracapsular cataract extraction and posterior chamber lens implantation markedly decreased the breakdown of the blood-

aqueous barrier. These authors did not comment on pupil size, but did note that postoperative IOP increase was not affected by this drug. In another study, flurbiprofen was also found to be effective in the treatment of contact lens-induced corneal neovascularization (Duffin et al., 1982b).

Another nonsteroidal drug, bendazac lysinate (benalin), which apparently has anti-denaturing activity on isolated proteins was recently used as an anti-cataract drug in clinical trials in Italy and was said to produce an actual reduction of in lens opacity in 22 patients, stability in 6 patients, while an increase in lens opacity was reported in only one of the patients (Testa et al., 1982). This effect, if it can be substantiated on larger populations, may be related to the direct auto-denaturing or anti-oxidant properties of this drug rather than on its potential effects on the AA cascade which is relatively inactive in the lens (Bazan H, 1989).

Anti-inflammatory drugs such as flurbiprofen (Weinreb et al., 1984) and indomethacin (Hotchkiss et al., 1974) were also tried following argon laser trabeculoplasty but these PG synthetase inhibitors did not significantly affect post-treatment inflammation especially the rise in IOP. However, it is noteworthy that among the flurbiprofen-treated patients, significantly fewer eyes had inflammation by 35 days after laser trabeculoplasty than did those in the vehicle-treated group (Weinreb et al., 1984). Persistent inflammation is a complication that is often difficult to manage effectively following laser trabeculoplasty. The apparent role of PGs in the ocular hypotensive effects of laser trabeculoplasty is discussed elsewhere in this volume (Camras and Podos, 1989).

Systemic aspirin has been used successfully to manage patients with vernal conjunctivitis (Giovanoni et al., 1984). Topically applied indomethacin, aspirin, or piroxicam, which are known to inhibit the formation of PGs, prostacyclins and TxA_2 through the cyclooxygenase pathway, significantly blocked conjunctival hyperemia and the mild chemosis produced by topical application of AA in normal human volunteers (Weston et al., 1984).

THE EFFECTS OF ANTI-INFLAMMATORY AGENTS ON CYSTOID MACULAR EDEMA (CME)

Another principal use of nonsteroidal anti-inflammatory agents is in the prevention and treatment of cystoid macular edema. The rationale for its use in this situation has to do with the finding that ocular inflammation such as that caused by intraocular surgery may raise PG levels in the eye, since intraocular inflammation shuts down the ocular PG transport system (Bito, 1973). The PGs are then thought to diffuse posteriorly toward the retina, causing a leak in the retinal vasculature that results in cystoid macular edema. Thus, preventing the synthesis of PGs should prevent the occurrence of cystoid macular edema (Miyake, 1977, 1978; Miyake et al., 1978; Shammas and Milkie, 1979; Weinreb et al., 1984; Hotchkiss et al., 1986).

However, it is not known whether PGs in the human eye are inactivated enzymatically or are removed by an absorptive transport process as was shown to be the case of the rabbit eye. Also, it is not known whether the human anterior uvea, like that of the rabbit lacks PG dehydrogenase or delta 9-reductase enzymes (Eakins et al., 1974) which inactivate PGs. Another unknown point is whether the accumulation of PGs in the aqueous humor of humans during or after uveitis is caused by the lack of a transport mechanism or by increased PG release into the aqueous humor.

To further support this hypothesis, not only is a demonstration of increased levels of PGs or LTs in ocular fluids following ocular surgery required, but also the demonstration that the increase in PG and LT levels is of sufficient magnitude to account for the observed effects. Nevertheless, several reports have indicated that oral or topical administration of indomethacin during the preoperative and postoperative period achieves long-term prevention of cystoid macular edema (Miyake, 1977, 1978; Miyake et al., 1978; Sholiton et al., 1978; Shammas and Milkie, 1979). However, indomethacin is apparently not effective in ameliorating cystoid macular edema once it has developed (Yannuzzi et al., 1977). These and more contemporary relevant observations are reviewed in detail in other chapters of this volume (Mishima et al., 1989; Schubert, 1989).

It is possible that long-term use or high doses of indomethacin may inhibit cyclooxygenase as well as lipoxygenase, and may activate phosphodiesterase-dependent metabolic pathways to ameliorate cystoid macular edema. In order to determine whether or not cyclooxygenase or lipoxygenase products are involved in the initiation of cystoid macular edema, further clinical studies using several other nonsteroidal drugs that interfere with AA metabolism but have different side effects are required. A recent study (Flach et al., 1987) demonstrated that the instillation of topical Ketorolac 0.5% four times daily for up to six months improves both visual acuity and angiographically recorded vessel leakage in eyes with cystoid macular edema. However, some caution must be used in interpreting these types of clinical studies, since suitable controls are not easily obtained and since the course of CME is highly unpredictable.

SUMMARY AND CONCLUSION

At the present time, corticosteroids are still the most effective class of drugs for the treatment of ocular inflammation. However, since their prolonged use may result in severe ocular side effects, it would be therapeutically beneficial to develop nonsteroidal anti-inflammatory drugs that have similar or greater efficacy than steroids, but do not share their ocular side effects. Several currently available nonsteroidal drugs have been used clinically as prophylactic or therapeutic agents for the following:

1. Prevention of pupillary constriction during intraocular surgery (cataract extraction).
2. Prevention of postoperative inflammation, i.e., incidence of anterior chamber cellular reaction and aqueous flare (breakdown of blood-aqueous barrier) and IOP rise following cataract surgery, intraocular lens implantation, and argon laser trabeculoplasty.
3. Prevention of contact lens induced corneal neovascularization.
4. Improvement of lens opacity (bendazac).
5. Prevention of cystoid macular edema following intraocular surgery. Treatment over long-term period may be effective; postoperative treatment is ineffective.
6. Prevention of conjunctival hyperemia.

Some prophylactic ocular uses such as prevention of surgical miosis or postoperative fluorescein leakage have been reported to be successful. However, it is unclear whether the reported success reflected the pharmacological effects due to inhibition of the AA cascade – and hence, reflects the role of some eicosanoids in surgical miosis or postoperative fluorescein leakage – or reflect the effects of these drugs on unexplored physiological or pharmacological mechanisms. For example, pretreatment with flurbiprofen to prevent surgical miosis was based on the assumption that PGs are potent miotic agents in all mammals, including humans. It remains to be established however, whether the small reduction in the extent of pupillary miosis is due to prevention of PG synthesis by this drug or to the prevention of the synthesis of other AA products, such as prostacyclin and thromboxane or possibly to some entirely different mechanism. Prevention of post-surgical fluorescein leakage by prophylactic pre and/or post surgical treatment with a variety of nonsteroidal anti-inflammatory agents is also assumed to be due to inhibition of intraocular PG synthesis, although the possibility that it is due to prevention of the synthesis of prostacyclin or TxA_2 has not been ruled out. Even more important, it has not been demonstrated that prevention of this post operative fluorescein leakage reflects the prevention or inhibition of true CME and associated loss of visual acuity. In fact, the results on the use of nonsteroidal anti-inflammatory agents once true CME has expressed itself remains controversial. In contrast, aggressive topical, periocular and systemic corticosteroid treatment has been reported to be beneficial in ongoing CME (Jaffe, 1984). Recently, diamox, a carbonic anhydrase inhibitor with no known anti-inflammatory effect has been reported to be effective against CME (Cox et al., 1988). If this observation can be substantiated, the proposed role of the AA cascade in CME would clearly require more careful scrutiny.

During the past decade, tremendous advances have been made toward a better understanding of the many components of the inflammatory process and the chemical mediators involved, including the various metabolites of AA. Currently available information suggest that such metabolites formed through the cyclooxy-

genase and lipoxygenase pathways play an important role in the modulation of the ocular inflammatory response. While there is ample evidence that some members of this cascade, especially certain leukotrienes, such as LTB_4, are pro-inflammatory, other members such as some stable prostaglandins can be demonstrated to be anti-inflammatory, or at least to limit some aspects of the inflammatory response (see also Bhattacherjee, 1989). Thus, the effective manipulation of the inflammatory response through manipulation of the AA cascade will depend on a better understanding of the role of each AA metabolite in various aspects of the inflammatory response and the development of specific inhibitors or antagonists that will allow the blocking of the synthesis, or the effects of individual products of this cascade. Such specific inhibitors may allow the blockade of adverse effects without jeopardizing the beneficial effects of other members of this cascade. Until then caution must be exercised in using inhibitors of one of the major AA metabolic pathways such as indomethacin, a cyclooxygenase inhibitor, because inhibition of one major AA metabolic pathway can be expected, and under some conditions have already been shown to enhance the synthesis of AA metabolite produced by other pathways. The resulting imbalance could – at least theoretically – be detrimental rather than beneficial.

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