likely site of action is the pigment epithelium. If so, these experiments provide evidence for an effect of light on the pigment epithelium without any corresponding changes in the neural retina. Given this, it seems possible that more intense exposure may exert its damaging effect on photoreceptors by first damaging the pigment epithelium.

Key words: ERG, rat retina, c-wave, light exposure, a-wave, b-wave

From the Departments of Ophthalmology, University of Michigan, Ann Arbor, and Henry Ford Hospital, Detroit, Michigan. Supported in part by NIH grant EY00379 and NEI training grant EY07022. Submitted for publication: February 6, 1984. Reprint requests: Daniel G. Green, Neuroscience Building, 1103 E. Huron, Ann Arbor, MI 48109.

References


5β-Dihydrocortisol: Possible Mediator of the Ocular Hypertension in Glaucoma

A. Louis Southren,*† Gary G. Gordon,* Danine I'Hommedieu,* Sunira Ravikumar,* Michael W. Dunn,† and Bernard I. Weinstein*†

5β-dihydrocortisol potentiates the action of topically applied dexamethasone in raising the intraocular pressure (IOP) in young rabbits. Dexamethasone (0.06%) plus 5β-dihydrocortisol (0.1 and 1.0%) elevated the IOP 7-10 mmHg within 18 days of treatment. By contrast, 0.06% dexamethasone alone raised the IOP 3 to 4 mmHg in a similar period of time. Since 5β-dihydrocortisol accumulates abnormally in cultured cells derived from the outflow region of the eye from patients with primary open angle glaucoma (POAG), a similar potentiation in man may account for the sensitivity of these patients to the IOP raising effect of glucocorticoids. Further, this metabolite may potentiate endogenous glucocorticoids resulting in the ocular hypertension characteristic of POAG. Invest Ophthalmol Vis Sci 26:393-395, 1985

Primary open angle glaucoma (POAG) is the most common form of glaucoma and a major cause of blindness. Most patients with POAG show a marked sensitivity to the intraocular pressure (IOP) raising effects of topical glucocorticoids.1-3 Evidence has accumulated suggesting that a glucocorticoid metabolite may play a role in the ocular hypertension and glucocorticoid sensitivity found in this disorder.4-6 Cells cultured from specimens obtained by trabeculectomy from patients with POAG (TMPOAG cells) showed an altered pattern of cortisol metabolism leading to the accumulation of both 5α and 5β-dihydrocortisol,4 intermediates not found in similar cells derived from nonPOAG patients.6 Assays of cortisol metabolizing enzymes in homogenates of TMPOAG cells, under optimal conditions, indicated that the accumulation of dihydrocortisol was due to alterations in two enzymes: a marked increase in cortisol Δ4-reductase and a decrease in 3-oxidoreductase.5 In acute experiments, 5β-dihydrocortisol (and not 5α-dihydrocortisol) was found to potentiate the cortisol and dexamethasone-induced nuclear translocation of the cytoplasmic glucocorticoid receptor in the rabbit, an early and necessary event in steroid hormone action.6

* Generic names of steroids: 5α (or 5β)-dihydrocortisol, 11β,17,21-trihydroxy-5α (or 5β)-pregnane-3,20-dione; dexamethasone (21-phosphate), 9-fluoro-16α-methyl-4β,17α,21-trihydroxy-1,4-pregnadiene (21-phosphate).
Fig. 1. Dose response of intraocular pressure (IOP) to dexamethasone in the rabbit. Intraocular pressure was measured in the rabbit after topical (ocular) administration of vehicle (phosphate buffered saline, PBS), varying concentrations of dexamethasone and dexamethasone phosphate (Decadron). Each point shown represents the mean IOP of four to six animals. The standard deviation of the means are shown for the last day of the experiment (day 18). Analysis of variance using the Bonferroni post-test showed that the IOP of the animals treated with 0.1% dexamethasone phosphate, 0.1% dexamethasone, and 0.06% dexamethasone were elevated significantly from the vehicle control (PBS) ($P < 0.01$, 0.01, and 0.05, respectively). The small elevation in IOP seen with 0.03% dexamethasone was not statistically significant.

We now report that chronic topical application of 5β-dihydrocortisol potentiates the intraocular pressure raising effect of threshold levels of dexamethasone in rabbits. This provides direct evidence in support of the hypothesis that 5β-dihydrocortisol mediates the sensitivity of POAG patients to exogenous glucocorticoids. Further, this metabolite may potentiate endogenous glucocorticoids resulting in the ocular hypertension characteristic of this disease.

Materials and Methods. Young New Zealand Albino rabbits weighing <2 Kg were used to test for biologic activity of 5β-dihydrocortisol since these animals have been reported to be consistently sensitive to the IOP raising effects of glucocorticoids. Animals were treated by placing 25 μl of the test solutions in each eye four times a day. Intraocular pressure was measured several times a week between 8 to 10 AM with an Alcon pneumotonometer (O.C.V.M. from Digilab Division of Bio-Rad) after addition of a topical anesthetic (tetracaine). A single mean value was used for each animal. Each group contained from four to six animals and the data reported are the mean IOP of each group. In one experiment with eight animals threshold levels of dexamethasone were administered bilaterally and 5β-dihydrocortisol unilaterally, four times daily. The steroids were suspended in phosphate buffered saline (PBS) by homogenization with a Teflon pestle. This produced a fine suspension of the steroids that minimized corneal irritation. The experiments were carried out in a masked fashion and conformed to the ARVO Resolution on the Use of Animals in Research.

Results and Discussion. Figure 1 shows the average IOP in groups of animals treated with varying concentrations of dexamethasone or with vehicle alone as a function of time. The animals treated with vehicle showed less than 2 mmHg variation in IOP during the entire course of the experiment. The dexamethasone-treated animals showed a dose response to the steroid with 0.1% dexamethasone and its phosphate ester (Decadron) significantly (see legend) raising IOP after 2 weeks of treatment while
0.06% dexamethasone showed a lesser but significant intraocular hypertensive response. Dexamethasone (0.03%) showed no significant elevation in IOP even after 18 days. Therefore, under these conditions of treatment, 0.06% dexamethasone was determined to be the threshold level of steroid for this response. In another experiment, varying concentrations of 5β-dihydrocortisol were given together with 0.06% dexamethasone. These results are shown in Figure 1 where the changes in IOP relative to the control group (PBS) are plotted as a function of day of treatment. Dexamethasone (0.06%) alone raised the IOP 3 to 4 mmHg within 2 weeks, similar to that seen in Figure 1. The addition of 5β-dihydrocortisol (0.1% and 1.0%) to the threshold level of dexamethasone produced a dose-related potentiation of the IOP raising effect of the steroid. Not shown are experiments in which 5β-dihydrocortisol (0.1 and 1.0%) by itself produced no change in IOP (<2 mmHg) even after 6 weeks of treatment. In another set of animals both eyes received 0.06% dexamethasone, and one eye received 0.1% (and later 0.2%) 5β-dihydrocortisol (Fig. 3). The eyes receiving 5β-dihydrocortisol had a significantly (see legend) greater IOP starting on day 16 of treatment. Thus, the potentiating effect of 5β-dihydrocortisol is, at least in part, a direct action of the metabolite on the ocular tissue. Figure 4 shows the specificity of the potentiation. In contrast to 5β-dihydrocortisol, 5α-dihydrocortisol (0.1%) did not significantly alter the IOP raising effect of 0.06 dexamethasone. Dexamethasone (0.1%) and dexamethasone (0.06%) plus a 0.1% 5β-dihydrocortisol-treated animals failed to gain—but did not lose—weight. The vehicle treated groups showed a steady weight gain during the course of these experiments.

These data suggest that 5β-dihydrocortisol, which accumulates abnormally in cultured cells derived from the outflow region of the eye from patients with POAG, is responsible for the sensitivity of these patients to exogenous glucocorticoids. Further, this metabolite may potentiate endogenous glucocorticoids, resulting in the ocular hypertension characteristic of POAG.

Key words: 5β-dihydrocortisol, cortisol metabolism, intraocular pressure, glaucoma

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