Intraocular Hypotensive Effect of a Topically Applied Cortisol Metabolite: 3α, 5β-Tetrahydrocortisol*

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3α,5β-tetrahydrocortisol, previously considered an inactive metabolite of cortisol, was found to lower significantly the intraocular pressure (IOP) of rabbits made ocular hypertensive with dexamethasone alone or with threshold levels of dexamethasone plus 5β-dihydrocortisol. The ocular hypotensive effect appeared within 3–7 days after the metabolite was started and persisted through the duration of the experiments. The metabolite did not lower the IOP of ocular normotensive untreated animals. Thus, 3α,5β-tetrahydrocortisol is a naturally occurring steroid antagonist, which may be of use in the treatment of primary open-angle glaucoma. Invest Ophthalmol Vis Sci 28:901–903, 1987

Recent studies have shown that young rabbits are consistently sensitive to the ocular hypertensive effect of topical glucocorticoids.1,2 The authors have found that the young rabbits are more sensitive during the fall and winter months. The accumulation of 5α- and 5β-dihydrocortisol in cultured cells derived from the outflow region of the human eye in primary open-angle glaucoma (POAG)3 and the finding that 5β-dihydrocortisol can potentiate the intraocular pressure (IOP) raising effect of topically applied dexamethasone in the rabbit2 makes this rabbit model particularly appropriate in evaluating antiglaucoma agents.

The authors now report that 3α,5β-tetrahydrocortisol, a cortisol metabolite previously considered to be biologically inactive, lowers the IOP of rabbits made ocular hypertensive with dexamethasone alone or with dexamethasone plus 5β-dihydrocortisol.

**Materials and Methods.** Young New Zealand white rabbits weighing about 1 kg were used. The animals were treated by placing 25 μl of the test solution on each eye four times a day, 7 days a week. IOP was measured several times a week in both eyes between 8–10 AM with an Alcon pneumatonometer (OCVM, from Digilab Division of BioRad, Cambridge, MA) after addition of a topical anesthetic (tetracaine). A single mean value was used for each animal. The steroids (Steraloids, Inc., Cambridge, MA) 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 of the Use of Animals in Research. Significance levels for IOP readings between groups of animals were determined for parametric data by analysis of variance followed by a Bonferroni post-test and for nonparametric data by the Mann Whitney rank sum test (an equivalent to the Wilcoxon rank sum).

**Results.** Figure 1 shows the average IOP data of a group of nine animals receiving 0.06% dexamethasone plus 0.1% 5β-dihydrocortisol and a group of six animals...
Fig. 2. The effect of 3α,5β-tetrahydrocortisol on the intraocular pressure (IOP) of rabbits made ocular hypertensive with 0.1% dexamethasone. The mean IOP is plotted as a function of days after beginning the tetrahydrocortisol therapy. Each point shown represents the mean IOP of all eyes treated in each group. The filled circles (● ●) represent the IOP of four rabbits continuing to receive 0.1% dexamethasone. The open circles (O — — O) represent the IOP of four animals treated with 0.1% dexamethasone plus 0.1% 3α,5β-tetrahydrocortisol. The filled squares (● □) represent five animals receiving phosphate buffered saline (vehicle control). Analysis by the Mann Whitney test indicates that tetrahydrocortisol caused a significant (P < 0.01) decrease in IOP.

Fig. 3. The effect of 3α,5β-tetrahydrocortisol on the intraocular pressure (IOP) of ocular normotensive rabbits. Each point represents the mean IOP of all eyes treated in each group. The filled circles (● — — ●) represent eight animals treated with 0.06% dexamethasone plus 0.1% 5β-dihydrocortisol. The open circles (O — — O) represent nine animals treated with 0.1% dexamethasone. The open circles (C — — C) represent five animals treated with 1% 3α,5β-tetrahydrocortisol and the closed squares (● □) represent five animals receiving phosphate buffered saline (vehicle control).

Animals made ocular hypertensive with 0.1% dexamethasone also responded with a statistically significant (P < 0.01) decrease in IOP after the addition of 0.1% 3α,5β-tetrahydrocortisol (Fig. 2).

Animals treated with 1% 3α,5β-tetrahydrocortisol alone showed no change in IOP during 19 days of treatment (Fig. 3). Steroid sensitivity of these animals was demonstrated by the fact that parallel groups of animals treated with (1) 0.1% dexamethasone or (2) 0.06% dexamethasone plus 0.1% 5β-dihydrocortisol responded with the expected increase in IOP of 5–8 mm Hg in 7–10 days.

Discussion. 3α,5β-tetrahydrocortisol has been shown to significantly lower the IOP in rabbits made ocular hypertensive with dexamethasone alone or with threshold levels of dexamethasone plus 5β-dihydrocortisol. The ocular hypotensive effect occurred in 3–7 days after 3α,5β-tetrahydrocortisol was started and persisted for the duration of the experiments (up to 17 days). Although the IOP did not reach the levels of the vehicle controls during the period of observation, there was no indication of tachyphylaxis during the experiment. The authors' data suggests that 3α,5β-tetrahydrocortisol may be a glucocorticoid antagonist in the target cells of the outflow region of the rabbit eye that are responsible for the glucocorticoid induced elevation of IOP. Progesterone, which is a partial glucocorticoid antagonist, has been reported to be acutely ocular hypotensive in the rabbit.4 More recently, the glucocorti-
ticoid antagonist RU484-6 was reported to produce a small hypotensive effect (0.5–2.5 mm Hg) in young pigmented normotensive rabbits. In the present study, however, 3α,5β-tetrahydrocortisol did not have an ocular hypotensive effect in the normotensive untreated rabbit eye.

3α,5β-tetrahydrocortisol is a normal metabolite in the human, and therefore may have low toxicity as an antiglaucoma agent. The delayed fall in IOP with this metabolite is comparable with the delayed rise in IOP seen with glucocorticoids. Steroid effects on IOP most likely occur through an alteration in composition of the extracellular matrix components in the outflow region and usually require from several days to a few weeks for their effects to be manifest. By contrast, agents that affect aqueous inflow or those that produce a mechanical effect on the outflow channels have a more immediate effect on IOP (min to hr).

Reduction of the A-ring is the first step in the inactivation and excretion of steroid hormones. Recently, however, A-ring reduced metabolites of cortisol, progesterone, and aldosterone have been shown to possess a variety of biologic activities that may be of physiologic significance. The present study provides evidence for an additional biological activity of a cortisol metabolite. This metabolite 3α,5β-tetrahydrocortisol, generally considered inactive, is a naturally occurring glucocorticoid antagonist that may be of use in the treatment of POAG.

Key words: ocular hypotensive effect, cortisol metabolite, 3α,5β-tetrahydrocortisol, POAG therapy

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