Drugs and the trabecular meshwork

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In primate eyes, most aqueous humor drainage is through the trabecular meshwork and inner wall of Schlemm’s canal and thence from the canal into collector channels and episcleral and conjunctival veins. In normal and open-angle glaucomatous eyes, most resistance to outflow is across the trabecular meshwork and inner canal wall. The ciliary muscle inserts at the scleral spur and trabecular meshwork. Contraction of the muscle markedly reduces outflow resistance, presumably by mechanically deforming the meshwork. Conversely, relaxation of the muscle increases outflow resistance. This anatomic relationship is manipulated to clinical advantage in the treatment of glaucoma with cholinomimetic drugs. However, it works to our disadvantage in the defining of physiologic effects of drugs directly on the trabecular meshwork and Schlemm’s canal, since a drug-induced change in outflow resistance could be due to drug-induced contraction or relaxation of the ciliary muscle.

A recently developed surgical technique for disinserting and retrodisplacing the entire ciliary muscle circumference from the scleral spur to a more posterior location on the sclera in the living monkey eye eliminates this problem. In “disinserted” eyes, aqueous humor leaves the anterior chamber via the trabecular meshwork and Schlemm’s canal in the normal manner, and the meshwork and canal appear normal by light and electron microscopy, and the retrodisplaced ciliary muscle contracts in the presence of pilocarpine. However, disinserted eyes show essentially no acute reduction in outflow resistance after intravenous or intracameral pilocarpine nor any resistance reduction after 18 to 24 hours of topical pilocarpine.
ually the entire outflow resistance-reducing effect of pilocarpine within the first 24 hours is mediated by ciliary muscle contraction, and apparently none by drug action directly on the conventional outflow channels.\textsuperscript{6, 13}

Topical or intracameral epinephrine decreases outflow resistance in rabbit and primate eyes.\textsuperscript{14-27} There is evidence for both alpha- and beta-adrenergic receptor-mediated resistance decreases.\textsuperscript{28-33} In recent years, it has become clear that at least beta-adrenergic receptors are present in a much wider variety of cells than previously suspected, including even neutrophils, erythrocytes, and lymphocytes.\textsuperscript{34} The ciliary muscle has relaxant beta-receptors.\textsuperscript{35} The resistance effects of adrenergic drugs might therefore be the resultant of effects on the ciliary muscle and effects on any of the endothelium-lined structures through which aqueous humor exits. Preliminary experiments indicate that intracameral epinephrine, norepinephrine, and cyclic AMP reduce total outflow resistance to a similar degree in disinserted and non-disinserted monkey eyes,\textsuperscript{30} eliminating at least the ciliary muscle as a major point of attack.

In monkeys, the endothelial cells of the inner canal wall and the adjacent meshwork contain cytoplasmic microfilaments and are suspected of contractibility.\textsuperscript{37, 38} Agents such as serotonin, histamine, bradykinin, and prostaglandins might therefore cause cell movement and separation, as in contractile vascular endothelium.\textsuperscript{39-42} Perhaps altering outflow resistance. Adrenergic agents might reduce resistance via a contractile mechanism.\textsuperscript{15} Since such drugs can also affect smooth muscle, disinserted eyes are proving valuable in localizing their effects on outflow resistance.\textsuperscript{31}

Cytochalasin B causes disruption of cytoplasmic microfilaments, thereby altering the shape and motility of many cell types.\textsuperscript{43} Intracameral infusion of microgram doses profoundly but reversibly reduces total outflow resistance in intact and disinserted monkey eyes.\textsuperscript{43} The decrease in total outflow resistance is due essentially entirely to decreased resistance to flow through the tissues between the anterior chamber and Schlemm’s canal.\textsuperscript{45} Electron microscopy demonstrates changes in the endothelial cells of the corneoscleral meshwork. More important in terms of outflow resistance, the endothelium of the inner wall of Schlemm’s canal contains increased numbers of transcellular aqueous pathways.\textsuperscript{46, 47} However, since most of the resistance to outflow is across the juxta-canalicular endothelial meshwork,\textsuperscript{35} the most important finding is loss of contact between the endothelial cells of this tissue, resulting in distention of the meshwork and washout of extracellular material.\textsuperscript{46, 47}

Isolated rabbit corneas perfused in a calcium-free medium demonstrate disruption of apical cytoplasmic microfilaments in the endothelial cells, accompanied by disintegration of endothelial cell junctions and separation of the cells.\textsuperscript{49-52} Intracameral infusion of the chelating agent EDTA in monkeys causes similar corneal endothelial changes\textsuperscript{47} and also greatly reduces outflow resistance through the conventional routes.\textsuperscript{52} Perhaps local calcium deficiency causes disruption of attachments between cells in the endothelial meshwork, leading to washout of extracellular material.

Based on the structure of the meshwork and the phagocytic properties of the meshwork endothelium described by Rohen, Bill has proposed the concept of the meshwork as a self-cleaning filter. Bill has suggested that insufficient self-cleaning, leading to an accumulation of debris clogging the filter and causing a rise in outflow resistance, might be the basis for the open-angle glaucomas.\textsuperscript{53} In monkeys there seems to be no permanent clinical damage to anterior ocular structures from one-time intracameral infusion of cytochalasin B.\textsuperscript{43} Bill theorizes that perfusion of the anterior chamber of glaucomatous human eyes at elevated intraocular pressure for a short time with a solution containing cytochalasin B or EDTA, or possibly one free of
calcium, might reversibly create new flow pathways through the meshwork and allow the accumulated debris to be washed downstream, perhaps providing many years of normalized outflow resistance and intraocular pressure. Might such a “pharmacological trabeculotomy” be a future treatment of certain glaucomas?

Hopefully, further advances in defining physiologic and morphologic responses of the trabecular meshwork and Schlemm’s canal to drugs may lead to new, potent antiglaucoma drugs and, eventually, to the discovery of the underlying biochemical, physiologic, and morphologic bases of the open-angle glaucomas.