Vanadate and aqueous humor dynamics

Proctor Lecture

Bernard Becker

Topical administration of 0.5% vanadate lowers intraocular pressure in monkey and rabbit eyes. This appears to be a consequence of a reduction in the rate of aqueous humor secretion, probably resulting from the inhibition of ciliary epithelium membrane NaK ATPase. The ubiquitous vanadate and its interactions with catecholamines and ascorbate may play a role in regulating the sodium pump of the ciliary epithelium. Adrenergic blocking agents may also lower intraocular pressure by inhibiting the NaK ATPase of the ciliary epithelium.

Key words: Vanadate, NaK ATPase, 86Rb accumulation, intraocular pressure, aqueous humor secretion, ascorbate, epinephrine, adrenergic antagonists

A few years ago a commercial preparation of adenosine triphosphate derived from rabbit or equine muscle was found to contain as an impurity a potent inhibitor of membrane sodium-potassium-dependent adenosine triphosphatase (NaK ATPase). Besides creating confusion among investigators and embarrassment for its St. Louis manufacturer, the incident led to a search for the identity of the inhibitor. The recent identification of the contaminant as the inorganic anion vanadate has stimulated considerable research on the biological actions of vanadium compounds. Since we knew from previous research that the enzyme NaK ATPase was in the ciliary epithelium of the rabbit eye and appeared to play a major role in the formation of aqueous humor, we tested the effects of vanadate on intraocular pressure. We found a decrease of intraocular pressure in rabbit and monkey eyes following the topical administration of vanadate solutions.

The present status of our studies on vanadate and aqueous humor dynamics provides the subject matter of this review. Although the work is still incomplete, I hope the preliminary results and the speculation arising from them prove of sufficient heuristic value to stimulate your thinking and your research efforts. The experimental work is a collaborative effort with Miss Carol Fritz and Drs. Theodore Krupin and Steven Podos.

Historical aspects

Vanadium is an ubiquitous element found in the earth’s crust, air, seawater, soil, and the tissues of man and animals. Concentrations in air are markedly increased in cities, especially in areas where there is combustion of petroleum fuel oils. The consumption by laboratory animals of as much as 3 /µg/gm in food and 5 /µg/ml in drinking water seems to have no inherent toxicity in terms of growth, longevity, or pathological changes. In fact, Nielsen and Sandstead conclude that vanadium is an essential trace element for rats and
chicks. Deficiency of vanadium results in reduced growth, sterility, increased plasma cholesterol, and poor bone development. In experimental animals, toxic doses produce vomiting, diarrhea, convulsions, and death by respiratory paralysis.9, 13, 16, 17

On usual diets, humans consume 1 to 4 mg of vanadium per day, particularly in gelatin, cereals, seafood, vegetables, and oils.9, 13 In human experiments no toxicity is noted after oral doses of 22 mg/day for 5 months except for the occurrence of a “green tongue.”14 In man 84% of acute doses are excreted in the urine and 7% in the feces, and only 9% is retained, largely in bones.15

The physiological and toxic actions of vanadium compounds were studied extensively as early as 1875. Gamgee and Larmuth16 recognized that vanadate acted on the heart very much like digitalis. Jackson17 described a profound diuresis following the administration of vanadate to animals. There followed a period at the turn of the century when, especially in France, oral vanadate was used not only as a “general tonic” but also as a panacea for heart disease, tuberculosis, syphilis, rheumatism, diabetes, arthritis, etc.18-20 It also was recommended as a local antiseptic for skin diseases.17 In more recent times Lewis21 noted that vanadate administered systemically lowered serum cholesterol levels in man.

Studies are now available which demonstrate a wide range of biochemical and pharmacological activities for vanadate. It inhibits several ATPases,22, 23 acid and alkaline phosphatases,24, 25 and adenylate kinase.26 It also decreases cholesterol synthesis27 and phosphofructokinase activity.28 However, vanadate stimulates adenylate cyclase.29 In addition, it affects glucose metabolism of many tissues.30 Vanadate stimulates glucose oxidation and transport in adipocytes much as does insulin or ouabain. It also increases glycogen synthesis in the liver and the diaphragm but inhibits intestinal glucose transport.

The systemic administration of vanadate produces a marked diuresis and natriuresis31 and increases the force of contraction of the heart (positive inotropic effect).32 Most significantly, vanadate is a reversible inhibitor of membrane NaK ATPase. It appears to bind to the cytoplasmic surface of the membrane.33, 34 This is in contrast to ouabain, which adheres to the extracellular membrane surface.

Membrane NaK ATPase

In 1957 Skou35 described an ATPase preparation from crab nerve membranes that was stimulated by sodium and potassium ions. He proposed that this enzymatic activity was associated with the physiological mechanism for active transport of monovalent cations, the plasma membrane sodium pump. Since that time the identification of NaK ATPase with the sodium-potassium pump has been generally accepted, and a wealth of information has accumulated about both the enzyme and the pump.36 The enzyme spans the lipid bilayer of many secretory cells as well as nervous tissues. The pump is oriented within the plasma membrane with a sodium activation site at the cytoplasmic surface and a potassium activation site at the extracellular surface. Ouabain is believed to prevent binding of potassium to the enzyme at the extracellular surface, whereas vanadate appears to act at the intracellular surface.

Table I. Agents which failed to alter ⁶⁸Rb accumulation by rabbit ciliary body (in vitro)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>10⁻³M-10⁻⁷M</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>10⁻⁴M-10⁻⁶M</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>10⁻⁴M-10⁻⁶M</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>10⁻³M-10⁻⁷M</td>
</tr>
<tr>
<td>Insulin</td>
<td>4 U/ml</td>
</tr>
<tr>
<td>Histamine</td>
<td>10⁻³M-10⁻⁶M</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>10⁻³M-10⁻⁶M</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>10⁻³M-10⁻⁶M</td>
</tr>
<tr>
<td>Ascorbate</td>
<td>10⁻³M-10⁻⁷M</td>
</tr>
<tr>
<td>Atropine</td>
<td>10⁻⁴M-10⁻⁶M</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>10⁻³M-10⁻⁴M</td>
</tr>
<tr>
<td>Cyclic AMP</td>
<td>10⁻³M-10⁻⁴M</td>
</tr>
<tr>
<td>Cyclic GMP</td>
<td>10⁻³M-10⁻⁴M</td>
</tr>
<tr>
<td>PGE₂</td>
<td>10⁻³M-10⁻⁶M</td>
</tr>
<tr>
<td>PGF₂β</td>
<td>10⁻³M-10⁻⁷M</td>
</tr>
<tr>
<td>Na nitroprusside</td>
<td>10⁻³M-10⁻⁴M</td>
</tr>
<tr>
<td>Azide</td>
<td>10⁻³M-10⁻⁶M</td>
</tr>
<tr>
<td>Phenytoin (Dilantin)</td>
<td>10⁻³M-10⁻⁷M</td>
</tr>
<tr>
<td>Anoxia (N₂)</td>
<td>10⁻³M-10⁻⁷M</td>
</tr>
<tr>
<td>Glucose-free media</td>
<td>10⁻³M-10⁻⁷M</td>
</tr>
</tbody>
</table>
Table II. Inhibitors of $^{86}$Rb accumulation by rabbit ciliary body (in vitro)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Concentration (50% inhibition)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ouabain</td>
<td>$1 \times 10^{-6}$M</td>
</tr>
<tr>
<td>Vanadate</td>
<td>$3 \times 10^{-3}$M</td>
</tr>
<tr>
<td>Prazosin</td>
<td>$1 \times 10^{-3}$M</td>
</tr>
<tr>
<td>Phenolamine</td>
<td>$7 \times 10^{-4}$M</td>
</tr>
<tr>
<td>Propranolol</td>
<td>$3 \times 10^{-4}$M</td>
</tr>
<tr>
<td>Timolol</td>
<td>$1 \times 10^{-5}$M</td>
</tr>
<tr>
<td>Cyanide</td>
<td>$1 \times 10^{-5}$M</td>
</tr>
<tr>
<td>Iodoacetate</td>
<td>$2 \times 10^{-2}$M</td>
</tr>
<tr>
<td>Dinitrophenol</td>
<td>$2 \times 10^{-2}$M</td>
</tr>
</tbody>
</table>

NaK ATPase and secretion of aqueous humor

Localization of enzyme in the ciliary epithelium. A ouabain-sensitive NaK ATPase has been demonstrated in the ciliary epithelium of cat, rabbit, and human eyes.\(^7\)\(^{37}\) Cytochemical localization of NaK ATPase in the nonpigmented ciliary epithelium was demonstrated by routine histochemistry\(^28\) and by electron microscopy.\(^39\)\(^{40}\) However, in these investigations, lead was used as the trapping ion. Lead not only inhibited the enzyme but also induced nonenzymatic hydrolysis of ATP. More recently, Ritch et al.\(^41\) have used the Ernst nitrophenylphosphate substrate with strontium as the capture ion. With this method reaction products were localized intracellularly, predominantly in the basolateral infoldings of the nonpigmented epithelial cells of the rabbit ciliary processes. Deposits were also noted in the basal infoldings of the pigmented epithelium. Treatment of specimens with ouabain or vanadate was demonstrated to reduce markedly the accumulation of reaction products.

$^{86}$Rb accumulation by rabbit ciliary body in vitro. Rabbit ciliary body–iris preparations incubated in vitro in Tyrode's solution at 37°C for 1 hr accumulate trace amounts of $^{86}$Rb to a concentration averaging 18 times that of the incubation medium. The uptake of $^{86}$Rb is time- and temperature-dependent. It is reduced to 25% of the 37°C value at 15°C and to 5% to 10% at 0°C. Sodium is required in the medium for accumulation of $^{86}$Rb to take place. The uptake is inhibited competitively by potassium, and saturation kinetics with nonlabeled rubidium can be demonstrated. The apparent Michaelis-Menten constant, $K_m$ (half-saturation concentration), approximates 3 mM Rb. Accumulation is not influenced by anoxia, lack of glucose, or the addition of epinephrine, norepinephrine, insulin, acetazolamide, ascorbate, atropine, acetylcholine, cyclic AMP, or cyclic GMP (Table I). A variety of metabolic inhibitors such as cyanide, iodoacetate, and dinitrophenol decrease the accumulation of $^{86}$Rb, but only in high concentrations (Table II).

The accumulation of $^{86}$Rb by the rabbit ciliary body–iris preparation can be inhibited most effectively by various concentrations of ouabain. The agreement between isolated enzyme inhibition and the reduction of $^{86}$Rb uptake suggests a close relationship of $^{86}$Rb accumulation and the NaK ATPase system of the ciliary body.\(^42\) In both instances, 50% inhibition is accomplished by approximately $1 \times 10^{-6}$M ouabain (Table II). The recent demonstration that vanadate can also inhibit $^{86}$Rb accumulation by the ciliary body is consistent with the role of NaK ATPase in this in vitro uptake. The considerably higher concentration of vanadate needed for inhibiting $^{86}$Rb uptake (50% inhibition at $3 \times 10^{-3}$M) may relate to the postulated intracellular site of action of vanadate on the enzyme.\(^33\) There may be difficulties in penetration of vanadate into the ciliary epithelial cell. Most important, the endogenous reducing substances in the cytoplasm may reduce the vanadate (+V oxidation state) to the vanadyl ion (+IV), a much less effective inhibitor of NaK ATPase.\(^34\)

The inhibition of $^{86}$Rb uptake in rabbit ciliary body–iris preparations by prazosin (Table II) is rather surprising. It is known that topical prazosin decreases the rate of formation of aqueous humor and lowers intraocular pressure in rabbit eyes.\(^43\) This is attributed to its action as an alpha-adrenergic blocking agent. The present observation raises the interesting question of possible inhibition of NaK ATPase and the sodium pump as the mechanism by which prazosin inhibits aqueous secretion. The similar inhibition of $^{86}$Rb accumulation by millimolar concentrations of the alpha-blocker phen-
Table III. Inhibition of aqueous humor flow 4 to 5 days after intravitreal injection of 0.5 μg of ouabain into rabbit eyes*

<table>
<thead>
<tr>
<th>Method</th>
<th>No. of animals</th>
<th>Flow inhibition (% ± σ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonography</td>
<td>20</td>
<td>68 ± 3.7</td>
</tr>
<tr>
<td>Ascorbate</td>
<td>20</td>
<td>72 ± 1.8</td>
</tr>
</tbody>
</table>

*Data from Becker B: INVEST OPHTHALMOL 2:325, 1963.

Table IV. Inhibition of aqueous humor flow 2 hr after topical 1% vanadate*

<table>
<thead>
<tr>
<th>Method</th>
<th>No. of animals</th>
<th>Flow inhibition (% ± σ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonography</td>
<td>12</td>
<td>32 ± 1.5</td>
</tr>
<tr>
<td>Ascorbate</td>
<td>9</td>
<td>38 ± 1.8</td>
</tr>
</tbody>
</table>

*Data from Krupin T, Becker B, and Podos SM: INVEST OPHTHALMOL VIS SCI (in press).

tolamine and by the beta-blockers propranolol and timolol further suggests that inhibition of the sodium pump may account for the ability of some adrenergic antagonists to reduce intraocular pressure.

Effects of ouabain. Ouabain inhibits NaK ATPase; this is true for the enzyme isolated from the ciliary epithelium. In addition, ouabain inhibits the histochemical localization and the ⁸⁶Rb accumulation by ciliary body in vitro as described above. Furthermore, ouabain lowers intraocular pressure following systemic administration to cats or rabbits. However, this occurs only at doses very close to levels toxic for the heart. Although ouabain does not lower intraocular pressure when applied topically, it is possible to inject small amounts into the vitreous cavity of rabbit eyes and obtain prolonged lowering of intraocular pressure. At 4 to 5 days after the injection of 0.5 μg of ouabain into the rabbit vitreous, intraocular pressure is reduced dramatically without significant change in outflow facility. Tonographically, one can estimate a 68% reduction in aqueous flow (Table III). Steady-state ascorbate concentrations in anterior and posterior chamber aqueous humor suggest a 72% reduction in the ratio of flow to diffusion coefficients for the anterior chamber (kᵣᵃ/kᵣₒᵤ) as compared to control eyes. This agrees well with the calculated NaK ATPase enzyme inhibition of 79%. In addition, the time course of the intraocular pressure fall and recovery after intravitreal ouabain correlates closely with the in vivo degree of inhibition of ciliary body NaK ATPase. No such changes in NaK ATPase concentration or ⁸⁶Rb uptake are noted after decreasing intraocular pressure by means of carbonic anhydrase inhibitors.

Recently "endigen" has been described as an endogenous physiological ligand that binds to ouabain receptors and inhibits NaK ATPase. It is partially purified from bovine hypothalamus, guinea pig brain, and mammalian heart. It inhibits ⁸⁶Rb uptake by human erythrocytes, blocks active sodium transport, and inhibits renal NaK ATPase. The existence of such a substance which imitates the actions of the digitalis glycosides raises interesting questions as to its role in the regulation of the sodium-potassium pump and the secretion of aqueous humor.

Effect of vanadate. As described above, vanadate is a potent inhibitor of the isolated enzyme NaK ATPase. It also reduces markedly the accumulation of reaction products in
Becker

October 1980

TOPICAL VANADATE & TOPICAL EPINEPHRINE
(30 Rabbits)

Fig. 2. Reversal of vanadate lowering of intraocular pressure in rabbits by topical administration of 2% epinephrine to one eye 60 min after topical 0.5% vanadate to both eyes.

Table V. Effect of topical vanadate on intraocular pressure in 5 rhesus monkeys

<table>
<thead>
<tr>
<th>Intraocular pressure (mm Hg)</th>
<th>Baseline</th>
<th>3 hr</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanadate, 0.5%</td>
<td>17.4 ± 1.0*</td>
<td>12.6 ± 1.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diluent</td>
<td>17.9 ± 1.0</td>
<td>17.4 ± 1.1</td>
<td>—</td>
</tr>
</tbody>
</table>

*Mean ± S.E.M.

the histochemical localization of the enzyme in the ciliary epithelium. Furthermore, it decreases the $^{86}$Rb uptake by the rabbit ciliary body in vitro. When applied topically to the rabbit eye in vivo, $^{48}$V-labeled vanadate can be demonstrated in the ciliary body in remarkably high concentrations 1 to 2 hr after administration. However, systemically administered $^{48}$V-labeled vanadate enters the rabbit eye poorly, and we are unable to lower intraocular pressure with sublethal doses of intravenous vanadate. In unanesthetized rabbits the topical administration of 0.5% or 1% vanadate lowers intraocular pressure significantly without alteration of episcleral venous pressure or outflow facility (Fig. 1). Tonographic estimates 2 hr after topical vanadate suggest a mean reduction in aqueous humor flow of 32% (Table IV). Similarly treated rabbits demonstrate significant increases in posterior chamber ascorbate concentration of the treated eyes compatible with a 38% mean decrease in the ratio of flow to diffusion coefficients for anterior chamber aqueous humor. Significant reductions in intraocular pressure are also obtained in rhesus monkey eyes following topical vanadate (Table V).

Since vanadate has many other biochemical and pharmacological activities, it is not established that the inhibition of NaK ATPase explains the reduction in aqueous secretion and fall in intraocular pressure that follows its topical administration. Although vanadate is a vasoconstrictor, the administration of phentolamine (5 mg/kg intravenously) 60 min be-
fore topical vanadate to one eye fails to prevent the lowering of intraocular pressure. Vanadate is said to stimulate adenylate cyclase, but we find no changes in aqueous humor cyclic AMP concentration or in outflow facility following topical vanadate. As mentioned above, vanadate inhibits some phosphatases and adenylate kinase and affects glucose metabolism and phosphofructokinase activity. Recent studies find that the vanadate stimulation of glucose oxidation in rat adipocytes, which mimics the effect of insulin, seems to be due mainly to the vanadyl (IV) ion. However, none of these effects can be demonstrated as the mechanism for altering the sodium pump in other tissues. The effects of vanadate on the kidney (diuresis and natriuresis) and the heart (positive inotropic effect) resemble those of digitalis and are best accounted for by inhibition of membrane NaK ATPase. Similarly, inhibition of NaK ATPase in the ciliary epithelium appears to be a reasonable working hypothesis for the mechanism by which vanadate lowers intraocular pressure.

**Vanadate and epinephrine**

In other tissues, an interaction between vanadate and catecholamines is described. The inhibition of NaK ATPase by vanadate is prevented or reversed promptly and completely by catecholamines in millimolar concentrations. This is postulated to be due to a complexation and direct chemical reduction of vanadate (V) to vanadyl (IV) by the
catecholamines, as evidenced by the yellow to brown color of the oxidized catecholamines or even the formation of a black precipitate. Several investigators have reported that NaK ATPase in brain tissue, muscle, erythrocytes, and kidney can be stimulated in vitro by biogenic amines such as dopamine, adrenaline, noradrenaline, and serotonin. The question is raised repeatedly as to whether this stimulation is a direct effect on the enzyme or due to a reduction by the catecholamines in the concentration of vanadate (V) in the tissue.

In the rabbit eye, we find that the intraocular pressure-lowering effects of vanadate are reversed promptly by topical epinephrine administration (Fig. 2). This may account for the observation that in rabbit and human eyes one often sees a transient elevation of intraocular pressure following topical epinephrine. Furthermore, Townsend and Brubaker describe increased secretion of aqueous humor following topical epinephrine administration to human eyes. The question must be raised as to whether epinephrine administration removes an endogenous vanadate inhibition of the sodium pump of the ciliary epithelium. In the absence of added vanadate there is no evidence that epinephrine or norepinephrine has a direct effect on ciliary epithelium NaK ATPase or that they alter Rb uptake by isolated rabbit ciliary body. However, these catecholamines in millimolar concentrations largely reverse the vanadate inhibition of Rb uptake by rabbit ciliary body in vitro. To date, the known effects of catecholamines on aqueous humor concentrations of cyclic AMP do not explain the transiently increased secretion, and cyclic AMP fails to affect Rb uptake. Although the effects of catecholamines on secretion of aqueous humor can be explained in other ways (e.g., prostaglandin-like effects), an alternative working hypothesis is that epinephrine administration may increase the secretion of the aqueous humor, at least transiently, by reducing the ever-present vanadate.

Fig. 4. Partial reversal of vanadate lowering of intraocular pressure in rabbits by systemic administration of ascorbate (50 mg/kg intravenously + 100 mg/kg subcutaneously) 60 min after topical 0.5% vanadate to one eye.
Vanadate and ascorbate

It is of considerable interest that the effects of vanadium on the sodium pump are dependent on its state of oxidation. Ascorbate is capable of reducing vanadate so that it no longer inhibits renal NaK ATPase. Although ascorbate does not alter $^{86}$Rb uptake by the rabbit ciliary body in vitro, the addition of millimolar concentrations of ascorbate reverses the inhibition of $^{86}$Rb accumulation by $3 \times 10^{-3}$M vanadate almost completely and partially restores the marked inhibition produced by $5 \times 10^{-3}$M vanadate (Table VI). Similarly, in the rabbit eye in vivo, although the subcutaneous or intravenous administrations of isotonic ascorbate fail to alter intraocular pressure significantly, the similar injection of ascorbate can largely prevent or partially reverse the lowering of intraocular pressure by topical vanadate (Figs. 3 and 4). Thus, in the eye, the high concentrations of ascorbate and its responsiveness to plasma levels may regulate the ciliary epithelial NaK ATPase inhibition by vanadate. Particularly in primates and man, who do not synthesize ascorbate, the effects of vanadate on the sodium pump of the ciliary epithelium may be influenced not only by dietary levels and accumulation of vanadium but also by variations in dietary ascorbate and its transport into the ocular fluids. In addition, there may be important vascular factors, for the level of ascorbate in the eye depends on the rate of blood flow through the ciliary body.

Speculation

As calculated by Cantley et al., a significant fraction of NaK ATPase should be inactive in vivo in most animals, including man, because of vanadate binding. Since vanadate is found in most mammalian tissues in concentrations of 0.1 to 1.0 $\mu$M and is so effective an inhibitor of NaK ATPase, suggestions are made repeatedly that vanadate may have a physiological role in controlling the rate of the sodium pump. This is postulated for kidney as well as other transport sites and offers attractive speculation about the regulation of secretion of aqueous humor. The vanadate concentration can be modified by dietary and other sources of vanadate intake as well as by its retention in tissues. It may be further changed abruptly by high concentrations of epinephrine. Especially in the eye, alterations in dietary ascorbate, ciliary body blood flow, and the transport of ascorbate into the eye may alter the oxidative state of vanadium and its ability to inhibit ciliary epithelium NaK ATPase.

One may speculate further about the interplay of vanadate and ascorbate on the variations in aqueous humor secretion that occur spontaneously, diurnally, and "protectively" (e.g., maintain lower intraocular pressure in spite of reduced outflow facility in some individuals with early primary open-angle glaucoma). The balance of vanadate and ascorbate may also contribute to the decline in secretion with age, to some instances of postoperative or posttraumatic hypotony, and to some eyes with advanced or "arrested" glaucoma.

Questions must also be raised about the therapeutic possibilities of using topical or dietary vanadate to lower intraocular pressure in glaucomatous eyes. Of course, one must first give serious consideration to possible systemic and ocular toxicity. Since the lens epithelium has a very effective NaK ATPase and its inhibition can result in cataracts, caution and careful long-term animal studies are indicated. Here again, the presence of high concentrations of ascorbate may well protect the lens. Similar reasoning applies for the corneal endothelium.

One may also speculate about the possible use of oral ascorbate to attempt to increase the rate of aqueous secretion in eyes where vanadate may be responsible for inhibiting the sodium pump. In this regard it is interesting that Friedenwald noted an increase in the rate of aqueous secretion in rabbits treated with large doses of ascorbate.

Finally, since both selected alpha and beta blocking agents can decrease the $^{86}$Rb uptake of ciliary epithelium, the possibilities must be explored that these agents reduce aqueous secretion and lower intraocular pressure by inhibition of membrane NaK ATPase of ciliary epithelium. This hypothesis does not...
deny the adrenergic blocking actions of these agents but does offer an alternative mechanism for their effects on intraocular pressure— one which avoids the conflict presented by adrenergic agonists and antagonists having the same effects on aqueous secretion.

REFERENCES


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