Intraocular pressure (IOP) is the most prevalent and only modifiable risk factor for the treatment of glaucoma, the leading cause of irreversible blindness. Current treatment modalities for glaucoma are aimed at lowering IOP of affected eyes with surgery, drugs, or both. Although surgical procedures lower IOP, their efficacy is variable and generally require additional procedures to maintain IOP reduction. Pharmaceutical agents used to treat glaucoma are also not effective in all cases and many of the commonly used drugs have unwanted side effects. Most importantly, current treatment modalities for glaucoma only delay the disease progression and do not cure it. Therefore, new agents need to be identified for improved management of glaucoma.

ATP-sensitive potassium (K\textsubscript{ATP}) channels connect the bioenergetic state of the cells to its membrane potential. Opening and closing of K\textsubscript{ATP} channels are known to affect contractility; leading cause of irreversible blindness. Current treatment cases and many of the commonly used drugs have unwanted additional procedures to maintain IOP reduction. Pharmaceutical agents for glaucoma only delay the disease progression and do not cure it. Therefore, new agents need to be identified for improved management of glaucoma.


**Purpose.** To evaluate the expression of ATP-sensitive potassium (K\textsubscript{ATP}) channel subunits and study the effect of K\textsubscript{ATP} channel openers diazoxide and nicorandil on intraocular pressure (IOP) in an in vivo mouse model.

**Methods.** Expression of K\textsubscript{ATP} channel subunits in normal C57BL/6 mouse eyes was studied by immunohistochemistry and confocal microscopy. Wild-type C57BL/6 mice were treated with K\textsubscript{ATP} channel openers diazoxide (n = 10) and nicorandil (n = 10) for 14 days. Similar treatments with diazoxide were performed on Kir6.2\textsuperscript{−/−} mice (n = 10). IOP was recorded with a handheld tonometer 1 hour, 4 hours, and 23 hours following daily treatment. Posttreatment histology was examined by light and transmission electron microscopy.

**Results.** The K\textsubscript{ATP} channel subunits SUR2B, Kir6.1, and Kir6.2 were identified in all tissues within mouse eyes. Treatment with diazoxide in wild-type mice decreased IOP by 21.5 ± 3.2% with an absolute IOP reduction of 3.9 ± 0.6 mm Hg (P = 0.002). Nicorandil also decreased IOP (18.9 ± 1.8%) with an absolute IOP reduction of 3.4 ± 0.4 mm Hg (P = 0.002). Treatment with diazoxide in Kir6.2\textsuperscript{−/−} mice had no effect on IOP. No morphological abnormalities were observed in diazoxide- or nicorandil-treated eyes.

**Conclusions.** K\textsubscript{ATP} channel openers diazoxide and nicorandil are effective regulators of IOP in mouse eyes. Kir6.2 appears to be a major K\textsubscript{ATP} channel subunit through which IOP is lowered following treatment with diazoxide.

Keywords: intraocular pressure, anterior segment, potassium channel

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**4892**
**TABLE 1.** Primary and Secondary Antibodies Utilized in Study

<table>
<thead>
<tr>
<th>Primary Antibodies</th>
<th>Source</th>
<th>Catalog Number</th>
<th>Secondary Antibodies</th>
<th>Source</th>
<th>Catalog Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit polyclonal anti-SUR1</td>
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<td>ab32844</td>
<td>Goat anti-rabbit IgG-AF 488</td>
<td>Invitrogen</td>
<td>A11008</td>
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<tr>
<td>Goat polyclonal anti-SUR2B</td>
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<td>sc32462</td>
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<tr>
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<tr>
<td>Rabbit polyclonal anti-Kir6.1</td>
<td>Abcam (Cambridge, MA)</td>
<td>ab80972</td>
<td>Goat anti-rabbit IgG-AF 488</td>
<td>Invitrogen</td>
<td>A11008</td>
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<tr>
<td>Rabbit polyclonal anti-Kir6.2</td>
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<td>NBP1-00900</td>
<td>Goat anti-rabbit IgG-AF 488</td>
<td>Invitrogen</td>
<td>A11008</td>
</tr>
</tbody>
</table>

Ophthalmic and Vision Research. All wild-type C57BL/6 mice (retired breeders, age > 8 months) were purchased from Charles River Laboratories (Wilmington, MA). Kir6.2<sup>−/−</sup> mice were gifts from Andre Terzic (Mayo Clinic, Rochester, MN). Mice were maintained in the Mayo animal care facility under a 12-hour light and dark cycle and received standard rodent chow and water ad libitum. Upon arrival, mice were housed for 5 to 10 days prestudy to acclimatize the animals to the housing conditions.

**Immunohistochemistry**

Emucellated eyes from untreated wild type C57BL/6 mice were used to study K<sub>ATP</sub> channel subunit composition. Eyes were fixed in 10% neutral buffered formalin (Fisher Scientific Inc., Kalamazoo, MI) for a minimum of 48 hours. Dissected tissues were dehydrated in an ascending series of ethanol concentrations (70%, 80%, 95%, and 100%), cleared in xylene and embedded in paraffin. Paraffin sections of 5 μm were mounted on glass slides (Superfrost/Plus; Fisher Scientific Inc.) and deparaffinized in xylene and rehydrated in a descending series of ethanol (100%, 95%, 80%, and 70%) followed by incubation in phosphate buffered saline. Antigen retrieval was performed by immersing the slides in 1 mM EDTA (pH 8.0) at 95°C for 30 minutes. Sections were blocked in 3% bovine serum albumin and 0.1% Tween 20 (Sigma-Aldrich, St. Louis, MO), and probed with antibodies against SUR1, SUR2B, Kir6.1, and Kir6.2 (Table 1). After being washed in PBS, sections were incubated with appropriate conjugated secondary antibodies (Table 1). Negative controls were incubated with only secondary antibodies. All sections were mounted with mounting media containing DAPI (Vycatsheild; Vector Laboratories, Burlingame, CA) and examined on a confocal laser microscope (Zeiss 510; Carl Zeiss Inc., Thornwood, NY). Fluorescent images were captured using the same digital settings for control and stained sections.

For immunostaining with SUR2A, eyes were immunostained in optimal cutting temperature (OCT) compound (Sakura Finetek USA Inc., Torrance, CA) and cryosectioned. Slides containing frozen sections were immersed in methanol for 20 minutes at −20°C, blocked in 3% BSA, and stained with SUR2A antibody (Santa Cruz Biotechnology, Dallas, TX) followed by AlexaFluor 568 conjugated secondary antibody (Table 1). Sections were mounted with media containing DAPI (Vector Laboratories) and examined by confocal laser microscopy as described above.

**IOP Measurements and Treatment**

After acclimatizing the mice in the housing facility, IOP was measured in conscious mice with a handheld rebound tonometer (Icare TonoLab; Colonial Medical Supply, Franconia, NH) once daily for a minimum of 3 days prior to the study to familiarize the animals to handling and IOP measurements. For IOP measurements, the tonometer was held so that the probe hit the cornea perpendicularly, as per the manufacturer’s instructions. The tonometer records six readings from the same eye, discards the highest and lowest values, and shows the average of the remaining four values as one IOP reading. Three independent measurements were averaged to obtain the IOP value at a given time point for each eye.

**Pretreatment.** IOP was measured in both mouse eyes three times daily for a period of 7 days. The IOP values for the three independent timepoints were averaged and recorded as the daily IOP.

**Diazoxide Treatment.** Diazoxide was prepared by diluting a 100 mM stock solution in 10% polyethylene glycol castor oil (Cremerophor EL; Sigma-Aldrich) in PBS. Use of polyethylene glycol castor oil helped maintain diazoxide in solution and served as a corneal permeabilization agent. In C57BL/6 wild-type (n = 10) and Kir6.2<sup>−/−</sup> (n = 10) mice, a 5-μL drop of 5 mM diazoxide was topically administered to one eye of each mouse while the fellow control eye received vehicle (DMSO and 10% polyethylene glycol castor oil in the same proportion as the treated eye). IOP was measured daily at 1 hour, 4 hours, and 23 hours following treatment. Average of the three IOP measurements was recorded as the daily IOP. Treatment with diazoxide and vehicle was continued daily for 14 consecutive days.

**Nicorandil Treatment.** In C57BL/6 mice (n = 10), one eye of each mouse was treated with nicorandil daily while the fellow eye received vehicle. Like diazoxide, nicorandil was prepared from a 100 mM stock solution (in DMSO), diluted in 10% polyethylene glycol castor oil to a final concentration of 5 mM. Nicorandil and vehicle treatments were provided daily for 14 consecutive days.

**Posttreatment.** Following the last day of treatment, several wild-type (n = 4 for diazoxide and n = 5 for nicorandil treatment) and Kir6.2<sup>−/−</sup> mice (n = 4) were killed by CO₂ asphyxiation. Both control and treated eyes were excised and placed in either 10% neutral buffered formalin or 4% paraformaldehyde in 0.1 M phosphate buffer. With the remaining wild-type (n = 6 for diazoxide and n = 7 for nicorandil treatment) and Kir6.2<sup>−/−</sup> mice (n = 6), treatment was stopped and IOP was measured three times daily for 7 consecutive days.

**Histology**

For eyes fixed in 10% neutral buffered formalin, whole eyes were dehydrated in a series of ascending ethanol concentrations, cleared in xylene, embedded in paraffin, sectioned at 5 μm, and mounted on glass slides (Fisher Scientific Inc.). For staining, sections were deparaffinized with xylene, rehydrated...
in descending series of ethanol, and rinsed in running distilled water. Sections were stained with hematoxylin (Electron Microscopy Sciences, Hatfield, PA); washed in running tap water, stained with eosin (Richard Allan Scientific, Kalamazoo, MI); and dehydrated in a series of ascending ethanol concentrations. Stained sections were placed in xylene and mounted under coverslips using a commercial micromount medium (Surgipath; Surgipath Medical Industries, Richmond, IL).

For transmission electron microscopy, whole eyes from diazoxide-treated wild-type mice (n = 2), diazoxide-treated Kir6.2 (/-/-) mice (n = 2), and nicorandil-treated mice (n = 1), fixed in 4% paraformaldehyde in 0.1 M phosphate buffer, were postfixed in osmium tetroxide, dehydrated in ascending ethanol concentrations, immersed in propylene oxide, and embedded in epoxy resin. Tissue blocks were sectioned at 100 nm, placed on copper grids, and stained with uranyl acetate and lead nitrate. Representative micrographs were taken at 35,000 magnification using a transmission electron microscope (JEOL 1400; JEOL USA Inc., Peabody, MA).

Statistics
All values are expressed as mean ± standard deviation. Analysis by Shapiro-Wilk test revealed several nonparametric data sets. Therefore, differences in IOP between treated and control eyes were compared using Wilcoxon rank sign test. Unpaired datasets were compared by Wilcoxon/Kruskal-Wallis tests (rank sums). P values were compensated for multiple comparisons using Bonferroni correction and results were considered significant when P < 0.002. All statistical calculations were performed using statistical software (JMP; SAS, Cary, NC).

Results
Kir6.2 Channel Subunits in the Mouse Eye
To evaluate which Kir channel subunits are present in the mouse eye, we performed immunohistochemistry on whole eye sections from untreated normal mice. Paraffin sections were used for staining SUR1, SUR2B, Kir6.1, and Kir6.2 (Fig. 1) while SUR2A was stained on frozen tissue sections (Fig. 2). No specific staining was observed for SUR1 (Figs. 1B, 1G, 1L) and SUR2A (Figs. 2B, 2D) in the various eye tissues that were studied. Only SUR2B of the sulfonylurea family and both Kir6.1 and Kir6.2 subunits of the Kir6 family were identified in the mouse eye (Figs. 1C–E, 1H–J). These subunits were also found to be present in the cells of the retina (Figs. 1M–O). SUR2B, Kir6.1, and Kir6.2 were present in the corneal epithelium and endothelium (Figs. 1C–E) as well as in many of the retinal cell layers (Figs. 1M–O). Although the inner and outer photoreceptor segments appeared to stain positive for all the SUR and Kir subunits, autofluorescence of the retinal pigments precluded us from confirming presence of the subunits in these layers since similar fluorescence was observed in the negative controls (Figs. 1K).

Figure 1. Expression profile of Kir channel subunits SUR1, SUR2B, Kir6.1, and Kir6.2. SUR1 was not present in mouse eye tissues (B, G, L). SUR2B, Kir6.1, and Kir6.2 were present in the trabecular meshwork (including inner and outer walls of Schlemm’s canal) C–E): corneal epithelium; TM, trabecular meshwork; CB, ciliary body; I, iris; AC, anterior chamber; GC, ganglion cells; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; IS, inner segments; OS, outer segments. Red fluorescence: SUR2B. Green fluorescence: SUR1, Kir6.1, and Kir6.2. Blue fluorescence: DAPI. Scale bar: 20 μm for all micrographs.
K<sub>ATP</sub> Channel Activation Decreases IOP In Vivo

**In Vivo Effect of Diazoxide Treatment on IOP**

Administration of diazoxide (5 mM) reduced IOP significantly within 48 hours of treatment in C57BL/6 wild-type mice (Fig. 3, black line). Comparison of the treated and control eyes at each timepoint (1 hour, 4 hours, and 23 hours) showed significantly lower IOP (*P* = 0.002, *n* = 10), suggesting that a single daily dose of diazoxide lowered IOP over a 24-hour period (Table 2). The daily absolute IOP reduction (average of 1 hour, 4 hours, and 23-hour timepoints) was 3.9 ± 0.6 mm Hg (*n* = 10 mice, *P* = 0.002) over the 14 days of treatment with a daily reduction range of 1.7 to 4.5 mm Hg (Fig. 5). This translates to a 21.5 ± 5.2% change in IOP compared with baseline with a daily IOP reduction range of 9.4 to 24.6%. Following treatment cessation, IOP of the treated eye returned to baseline levels within 48 hours (*P* > 0.002 for IOP comparisons between treated and control eyes).

To confirm specificity and determine subunit importance, we evaluated the effect of diazoxide on IOP in C57BL/6 mice lacking the K<sub>6.2</sub> subunit. No statistical difference was observed in baseline IOP between the right (15.8 ± 0.6 vs. 17.2 ± 1.1 mm Hg, *P* = 0.006; *α* = 0.005 after multiple comparison correction) and left (15.7 ± 0.7 vs. 17.2 ± 1.2, *P* = 0.009) eyes of wild-type and K<sub>6.2</sub><sup>−/−</sup> mice (*n* = 10 wild-type and *n* = 10 K<sub>6.2</sub><sup>−/−</sup> mice). However, unlike the wild-type mice, DZ did not lower IOP in the K<sub>6.2</sub><sup>−/−</sup>-treated eyes at 1 hour, 4 hours, and 23 hours following treatment (Table 2, *P* > 0.002, *n* = 10). The average daily IOP difference between treated and control eyes was 0.4 ± 0.7 mm Hg (Fig. 3, gray line, *P* = 0.03). In these animals, IOP remained stable and did not show any variation from baseline during treatment with

### Table 2. Effect of K<sub>ATP</sub> Channel Opener Treatment on IOP

<table>
<thead>
<tr>
<th></th>
<th>Wild Type C57BL/6 (n = 10)</th>
<th>K&lt;sub&gt;6.2&lt;/sub&gt;&lt;sup&gt;−/−&lt;/sup&gt; (n = 10)</th>
<th>Nicorandil Treated&lt;sup&gt;+&lt;/sup&gt; (n = 10)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ΔIOP ± SD, mm Hg</td>
<td>% Change Compared With Control ± SD</td>
<td>ΔIOP ± SD, mm Hg</td>
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<tr>
<td>1 h</td>
<td>3.9 ± 0.7†</td>
<td>−21.3 ± 3.2</td>
<td>−0.6 ± 0.8</td>
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<tr>
<td>4 h</td>
<td>3.9 ± 0.9†</td>
<td>−21.7 ± 4.6</td>
<td>−0.2 ± 0.7</td>
</tr>
<tr>
<td>23 h</td>
<td>3.8 ± 0.9†</td>
<td>−21.6 ± 4.9</td>
<td>−0.5 ± 0.6</td>
</tr>
<tr>
<td>Average</td>
<td>3.9 ± 0.6†</td>
<td>−21.5 ± 3.2</td>
<td>−0.4 ± 0.7</td>
</tr>
</tbody>
</table>

SD, standard deviation.

<sup>+</sup> Numbers represent average of 14-day treatment period.

<sup>†</sup> *P* = 0.002.
Effect of Nicorandil Treatment on IOP

In previous studies on human ex vivo eye cultures, we found that in addition to diazoxide, nicorandil also decreased IOP and increased outflow facility. To confirm this in vivo, we used the same experimental design as mentioned above for diazoxide. Similar to what we found with diazoxide, nicorandil-treated C57BL/6 wild-type mice eyes (n = 10) showed a significant reduction in IOP at 1 hour, 4 hours, and 23 hours compared with control (Table 2). Daily IOP values decreased by 3.4 ± 0.4 mm Hg (P = 0.002; Fig. 5) during the 14-day treatment with a daily reduction range of 2.0 to 3.9 mm Hg. This constituted an 18.9 ± 1.8% change between nicorandil-treated and control eyes with a daily reduction range of 12.0 to 21.2%. On completion of the 14 days of treatment, IOP returned to baseline within 48 hours (P > 0.002 for IOP comparisons between control and treated eyes on all posttreatment days). Similar to diazoxide treatment, histologic examination of the eye following nicorandil treatment did not show any adverse side effects to the tissues and cells of the outflow pathways (Figs. 6A–D).

Effect of Diazoxide Treatment on Ocular Histology of C57BL/6 Mice

Diazoxide treatment with diazoxide had no observable changes in cell and tissue appearance within the conventional outflow pathway following diazoxide treatment as evident from H&E staining (Figs. 4A–D) and transmission electron microscopy (Figs. 4E–H). Scale bar: 50 μm for H&E and 5 μm for transmission electron microscopy.

diazoxide. Similar levels of K\textsubscript{ir}6.1 subunits were identified in K\textsubscript{ir}6.2\textsuperscript{−/−} (Supplementary Figs. 1A–F) and wild-type animals, suggesting the knockout of K\textsubscript{ir}6.2 did not influence expression of K\textsubscript{ir}6.1.

Histologic evaluation of ocular tissues within the outflow pathway following diazoxide treatment was performed using hematoxylin and eosin (H&E) staining (Figs. 4A–D) and by transmission electron microscopy (Figs. 4E–H). In wild-type and K\textsubscript{ir}6.2\textsuperscript{−/−} mice, there were no structural changes in the anatomy of the outflow pathways. Both the trabecular meshwork and the inner and outer wall of Schlemm’s canal appeared normal with similar numbers of viable cells. Overall, treatment with diazoxide or vehicle had no observable changes to cell and tissue histology within the outflow pathway (Figs. 4A–H).

DISCUSSION

Current pharmaceutical treatments for glaucoma are often inadequate in patients due to ineffectiveness of the drugs to lower IOP, side effects, or inability of the drugs to address visual field loss. Development of drugs that lower IOP by targeting underlying physiological processes will be helpful in minimizing vision loss. In this study, we characterized the presence of K\textsubscript{ATP} channel subunits in the mouse eye and showed that activation of these channels by K\textsubscript{ATP} channel openers diazoxide and nicorandil are effective at reducing IOP. Additionally, we identified the K\textsubscript{ir}6.2 subunit as a necessary component for IOP modulation through K\textsubscript{ATP} channels. Results from the current study, along with our previous findings that diazoxide and nicorandil increase outflow facility in ex vivo human anterior segments, indicate that K\textsubscript{ATP} channel openers may be a new class of ocular hypotensive agents.

K\textsubscript{ATP} channels contain four identical SUR subunits (SUR1, SUR2A, or SUR2B) and four identical K\textsubscript{ir} subunits (K\textsubscript{ir}6.1 or K\textsubscript{ir}6.2), making multiple K\textsubscript{ATP} channel subtypes based on subunit composition possible (e.g., SUR1/K\textsubscript{ir}6.1, SUR2A/K\textsubscript{ir}6.2, SUR2B/K\textsubscript{ir}6.1 etc). The heterogeneity of K\textsubscript{ATP} channels imparts considerable differences to their pharmacologic properties. Nevertheless, most K\textsubscript{ATP} channel openers are specific for K\textsubscript{ATP} channels with a particular combination of SUR and K\textsubscript{ir} subunits. Diazoxide has minimal to no effect on K\textsubscript{ATP} channels...
**Figure 6.** Histology of nicorandil-treated C57BL/6 mice eyes. Ocular morphology of the tissues and cells of the conventional outflow pathway appeared similar between treated and control eyes by either H&E (A, B) or transmission electron microscopy (C, D). Scale bar: 50 μm for H&E and 5 μm for transmission electron microscopy.

Channels have not been identified in vivo, in vitro studies have suggested that single K<sub>ATP</sub> channel openers may be the cause of IOP reduction. Even in normotensive mice, failure of diazoxide to lower IOP by 3.5 mm Hg necessitates the presence of other channels that may contribute to IOP regulation. A subunit containing SUR2A/K<sub>ATP</sub>6.1 and K<sub>ATP</sub>6.2 are possible. However, while these studies have shown that single channel openers can lower IOP, the exact subunit structure making up K<sub>ATP</sub> channels involved in IOP regulation will be important for future drug development.

The K<sub>ATP</sub>6.2<sup>−/−</sup> mice used in this study have been extensively characterized<sup>44</sup> and have been used as a viable mouse model to study cardioprotection, glucose metabolism and insulin secretion,<sup>11,12,23,44,45</sup> with K<sub>ATP</sub>6.2<sup>−/−</sup> mice being susceptible to stress and cardiac overload and have defective glucose-dependent insulin secretion along with increased numbers of β-cells and pancreatic polypeptide positive cells in the pancreatic islets.<sup>23,46</sup> These mice have been backcrossed to mice from the C57BL/6 background for multiple generations and hence age-matched C57BL/6 mice were used as wild-type controls for studies involving these knockouts.<sup>23,45,47</sup> Overall, under normal conditions, the K<sub>ATP</sub>6.2<sup>−/−</sup> mice appear normal and are fertile with no significant differences in body weight, behavior, or appearance when compared to the wild type.<sup>44</sup>

Because of the lack of an ocular hypertension model to study drugs that affect the outflow pathways, we were limited to analyzing the effect of K<sub>ATP</sub> channel openers on normotensive animals. In normal mice, all commonly used antiglaucoma agents have been shown to lower IOP; therefore, treating normotensive mice to study efficacies of ocular hypotensive agents is an established practice.<sup>48,49</sup> For example, the prostaglandin analog latanoprost has been shown to lower IOP by 20% in the presence of normal retinal nerve fiber layer thickness and in IOP between treated and control eyes of 18%.<sup>50,51</sup> In our study, both diazoxide and nicorandil decreased IOP by approximately 20% with absolute IOP change of 3.9 ± 0.6 and 3.4 ± 0.4 mm Hg, respectively, suggesting K<sub>ATP</sub> channel openers have a similar IOP reduction to current antihypertensive agents used to treat glaucoma. Furthermore, both diazoxide and nicorandil were found to significantly lower IOP at individual time points (1 hour, 4 hours, and 23 hours) suggesting that a single daily dose of diazoxide or nicorandil has immediate and lasting effects on IOP.

Previous studies from our laboratory have shown that diazoxide and nicorandil lowered IOP in ex vivo human anterior segment cultures through the conventional outflow pathway.<sup>52</sup> Functional similarities exist between human and mouse eyes and drugs affecting the conventional pathway in human eyes have been shown to retain their mode of action in mouse eyes.<sup>50</sup> In light of this, there is a strong possibility that diazoxide and nicorandil, which work through the conventional outflow pathway in human eyes, are also affecting the conventional pathway in mice. However, the presence of K<sub>ATP</sub> channel subunits throughout the human and mouse eye suggests that K<sub>ATP</sub> channel openers may also alter unconventional flow and possibly aqueous inflow. Studies assessing aqueous humor dynamics in these mice following K<sub>ATP</sub> channel opener treatment will be necessary to elucidate the specific inflow and outflow pathways involved in K<sub>ATP</sub> channel modulated IOP reduction.

It should be noted that in primary open-angle glaucoma (POAG) patients, an acceptable reduction in IOP with a therapy of frontline drugs is around 20%.<sup>51</sup> Combination of multiple medications is often required to achieve a target IOP in POAG patients.<sup>52</sup> We have shown that diazoxide, when used in combination with latanoprost free acid, shows an additive effect in reducing pressure in human anterior segment cultures (Roy Chowdhury U, et al. IOVS 2011;52:ARVO E-Abstract 4642), indicating that K<sub>ATP</sub> channel openers may be future candidates for combination therapy for POAG. Of further interest is the fact that K<sub>ATP</sub> channel openers have been shown to provide retinal neuroprotection in rat models.<sup>53,54</sup> Given the fact that none of the existing glaucoma medications protect the retina from degeneration, K<sub>ATP</sub> channel openers may be the treatment of choice for glaucoma.
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first drug of its class that shows both hypotensive and neuroprotective properties.

In summary, our study indicates a specific ocular hypotensive effect of K$_{\text{ATP}}$ channel openers diazoxide and nicorandil in an in vivo murine model. Our data suggest that diazoxide and nicorandil work through the K$_{6.2}$/SUR2B subunit. Considering that diazoxide and nicorandil act only on SUR2B containing K$_{\text{ATP}}$ channels, it is reasonable to conclude that K$_{\text{ATP}}$ channels composed of K$_{6.2}$/SUR2B are the primary subunit combination involved in K$_{\text{ATP}}$-channel-mediated IOP regulation. Although further work is needed to elucidate the exact cellular pathways linking KATP channels to IOP reduction, there is a strong potential for these openers to become future therapeutic agents for the treatment of ocular hypertensive diseases like POAG.

Acknowledgments

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References


