Optic nerve transection and intraocular pressure response to various drugs

Steven M. Podos, Theodore Krupin, and Bernard Becker

Base-line intraocular pressure was similar in the rabbit eye with a transected optic nerve and the opposite eye subjected to a sham operation. Hyperosmotic oral ethanol, at doses of 1.5 to 2.0 ml. per kilogram, lowered intraocular pressure significantly less in eyes with transected optic nerves than in their fellow eyes with intact optic nerves. Smaller doses of ethanol (0.75 ml. per kilogram) decreased intraocular pressure only in sham-operated eyes. Topically applied pilocarpine or epinephrine hydrochloride produced no difference between the intraocular pressures of the two eyes. Intravenous acetazolamide lowered intraocular pressure symmetrically in eyes with both intact and transected optic nerves.

Key words: optic nerve transection, intraocular pressure response, ethanol, pilocarpine, epinephrine, acetazolamide, osmotic stimuli.

In a previous study, optic nerve transection in rabbits was found to diminish the homolateral responses of intraocular pressure to osmotic stimuli, such as the ingestion of water or hypertonic isosorbide. The response in the eye with optic atrophy was significantly less than that of the sham-operated contralateral eye of the same rabbit. No difference in base-line intraocular pressure between the two eyes was noted. The intraocular pressure response to a variety of other agents using the same experimental model is the subject of this report.

Material and methods

Surgical transection of the optic nerve was performed on one eye of rabbits and a sham procedure on the fellow eye. The operative procedures, criteria for utilization, and techniques for measurement of intraocular pressure and outflow facility using topical anesthesia alone were previously described. The blood supply to the extraocular muscles was not interrupted. Care was taken to avoid damaging neighboring vessels accompanying the optic nerve and the central retinal artery which enters the optic nerve close to the globe. Animals were not used until at least one month after transection.

Several drugs were tested. Ethanol, 50 per cent, was administered by oral-gastric tube, in doses of 0.75, 1.5, and 2.0 ml. per kilogram of body weight. Schiötz tonometry was done before and 1 and 2 hours after administration. Pilocarpine, 4 per cent drops, was applied topically to both eyes 4 times a day for 4 days, and tonography was carried out two hours after the last drop. Epinephrine hydrochloride, 2 per cent drops, was applied topically to both eyes 4 times a day for 2 days, and tonography was carried out 2 hours after the last drop. Acetazolamide (Diamox), 50 mg. per milliliter, was administered intra-
Table I. Alterations of intraocular pressure induced by ethanol (50 per cent) in rabbits eyes subjected to optic nerve transection or sham operation

<table>
<thead>
<tr>
<th>ml/Kg (oral)</th>
<th>Time (hr.)</th>
<th>No. of animals</th>
<th>Optic nerve cut (Mean ± S.E.M.)</th>
<th>Sham operation (Mean ± S.E.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>P₀</td>
<td>P₁</td>
</tr>
<tr>
<td>0.75</td>
<td>1</td>
<td>8</td>
<td>16.5±0.9</td>
<td>15.6±0.9</td>
</tr>
<tr>
<td>1.5</td>
<td>1</td>
<td>10</td>
<td>19.3±1.1</td>
<td>16.7±1.1</td>
</tr>
<tr>
<td>2.0</td>
<td>1</td>
<td>8</td>
<td>20.2±0.8</td>
<td>17.1±0.8</td>
</tr>
<tr>
<td>2.0</td>
<td>2</td>
<td>8</td>
<td>20.2±0.8</td>
<td>16.8±0.8</td>
</tr>
</tbody>
</table>

P₀ is initial intraocular pressure in mm. Hg, P₁ is intraocular pressure at designated times after ethanol, ΔP is P₁-P₀ (mean of individual differences).

Table II. Statistical results of paired t tests for intraocular pressure after ethanol (50 per cent)

<table>
<thead>
<tr>
<th>Body weight ml/Kg (oral)</th>
<th>Time (hr.)</th>
<th>No. of animals</th>
<th>Optic nerve cut P₁ vs. P₀</th>
<th>Sham operation P₁ vs. P₀</th>
<th>Cut vs. sham ΔP cut* vs. ΔP sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75</td>
<td>1</td>
<td>8</td>
<td>0.3&gt;p&gt;0.2</td>
<td>p&lt;0.001</td>
<td>0.001&lt;p&lt;0.005</td>
</tr>
<tr>
<td>1.5</td>
<td>1</td>
<td>10</td>
<td>0.005&lt;p&lt;0.01</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>2.0</td>
<td>1</td>
<td>8</td>
<td>0.005&lt;p&lt;0.01</td>
<td>p&lt;0.001</td>
<td>0.001&lt;p&lt;0.005</td>
</tr>
<tr>
<td>2.0</td>
<td>2</td>
<td>8</td>
<td>0.001&lt;p&lt;0.005</td>
<td>p&lt;0.001</td>
<td>0.001&lt;p&lt;0.005</td>
</tr>
</tbody>
</table>

*ΔP cut is P₁ cut - P₀ cut; ΔP sham is P₁ sham - P₀ sham.

venously in doses of 100, 50, 25, and 10 mg. per kilogram of body weight. Schi0tz tonometry was done before and 30 and 60 minutes after administration.

Statistical evaluation was performed on all data using the paired t test.

Results

Before the use of any drug, no significant differences in initial intraocular pressures or outflow facilities were noted between the eyes with transected optic nerves and their sham-operated mates.

Ethanol. The mean intraocular pressures before and at different times after ingestion of various amounts of 50 per cent ethanol are presented in Table I. Decreases of intraocular pressure were noted after larger doses (1.5 and 2.0 ml. per kilogram) in both groups of eyes. However, the diminution of intraocular pressure in the transected optic nerve group was significantly less than that in the sham-operated group for all doses and times tested (p < 0.005). Administration of smaller amounts of alcohol (0.75 ml. per kilogram) produced a significant decrease in intraocular pressure only in the sham-operated intact eyes (Table II).

Topical therapy. Pretreatment with 4 per cent pilocarpine or 2 per cent epinephrine hydrochloride to both eyes of rabbits produced no difference between cut and sham groups with respect to mean intraocular pressure and mean outflow facility (Table III).

Acetazolamide. Table IV lists the mean intraocular pressure before and 30 and 60 minutes after intravenous administration of various doses of acetazolamide for both groups of eyes. A diminution of pressure occurred (p < 0.005) in both the eyes with transected optic nerves and the eyes with intact optic nerves, but the changes in intraocular pressure were not significantly different comparing the two eyes of animals for all doses and times.
Table III. Effect of topical therapy on intraocular pressure of rabbit eyes subjected to optic nerve transection or sham operation

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of animals</th>
<th>Optic nerve cut (Mean ± S.E.M.)</th>
<th>Sham operation (Mean ± S.E.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocarpine 4%*</td>
<td>9</td>
<td>16.4 ± 1.2</td>
<td>17.0 ± 0.8</td>
</tr>
<tr>
<td>Epinephrine 2%*</td>
<td>12</td>
<td>20.2 ± 0.8</td>
<td>19.0 ± 0.2</td>
</tr>
</tbody>
</table>

P<sub>i</sub> (intraocular pressure in mm. Hg) and C<sub>i</sub> (outflow facility) are measured 2 hours after last drop of 4 days of pilocarpine and 2 days of epinephrine in a group of animals with no initial difference between sham-operated and optic nerve-cut eyes.

*No significant difference between P<sub>i</sub> cut and P<sub>i</sub> sham or C<sub>i</sub> cut and C<sub>i</sub> sham.

Table IV. Effect of acetazolamide on intraocular pressure of rabbit eyes subjected to optic nerve transection or sham operation

<table>
<thead>
<tr>
<th>mg/Kg*</th>
<th>Time (hr.)</th>
<th>No. of animals</th>
<th>Optic nerve cut (Mean ± S.E.M.)</th>
<th>Sham operation (Mean ± S.E.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>P&lt;sub&gt;i&lt;/sub&gt;</td>
<td>P&lt;sub&gt;o&lt;/sub&gt;</td>
</tr>
<tr>
<td>100</td>
<td>1</td>
<td>8</td>
<td>17.6 ± 0.6</td>
<td>10.5 ± 1.4</td>
</tr>
<tr>
<td>50</td>
<td>1</td>
<td>8</td>
<td>16.8 ± 0.8</td>
<td>10.1 ± 0.7</td>
</tr>
<tr>
<td>25</td>
<td>1</td>
<td>8</td>
<td>17.8 ± 1.2</td>
<td>12.6 ± 1.1</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>8</td>
<td>14.8 ± 0.7</td>
<td>12.9 ± 0.3</td>
</tr>
</tbody>
</table>

P<sub>i</sub> is initial intraocular pressure in mm. Hg, P<sub>o</sub> is intraocular pressure at designated time after Diamox administration. ΔP is P<sub>i</sub> - P<sub>o</sub> for cut and sham eyes.

*No significant difference between ΔP cut and ΔP sham for any dose or time.

Comment

The actions of isosorbide and water on intraocular pressure are presumed to be related to their osmotic effects. A decreased intraocular pressure response to water ingestion is noted in human eyes after optic nerve lesions. In the rabbit, optic nerve transection limits the intraocular pressure changes induced by these agents without altering base-line aqueous humor dynamics. Ethanol also appears to lower intraocular pressure by directly raising serum osmolarity and later perhaps by inhibiting antidiuretic hormone. In the present study, eyes with cut optic nerves demonstrate lesser responses to ethanol than the control fellow eyes. At low levels of osmotic stress only the intact (sham-operated) eyes show a fall in pressure. Efferent fibers are documented in the optic nerve of rabbit and man. It has been suggested that osmotic stimuli may affect aqueous humor dynamics via some efferent fibers associated with the optic nerve, possibly from the hypothalamus. It is of interest that antidiuretic hormone also originates in the hypothalamus.

Other antiglaucomatous therapies, without osmotic effects, do not alter intraocular pressure differentially in rabbit eyes with transected optic nerves as compared to their sham-operated mates. Pilocarpine and epinephrine, applied topically, produce no differences between the two groups. Acetazolamide, 100 mg. per kilogram intravenously, decreases rabbit intraocular pressure within one hour. The decrease is similar in cut and sham eyes in...
the present study. It would thus appear that the lowering of intraocular pressure by carbonic anhydrase inhibitors is not dependent upon an intact optic nerve.

REFERENCES