A second component of atropine mydriasis.

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A patient with Waardenburg syndrome had, in addition to the classical findings, a semifixed pupil which did not react to changes of illumination, to convergence, or to pilocarpine or phospholine iodide. However, it responded normally to locally applied drugs acting on the sympathetic system. The pupil dilated after application of atropine, homatropine, or cocaine. The effect of cocaine, but not of atropine and homatropine, was prevented by pretreatment with guanethidine. It is concluded that the mydriasis caused by atropine and homatropine is partly dependent upon a direct action on the radial smooth muscle.

The iris has been used repeatedly for examining autonomic functions in human beings\(^1\)\(^-\)\(^3\) as well as the pharmacologic actions of drugs.\(^4\)\(^-\)\(^6\) The direct measurement of the response, through pupil size, and the ease with which drugs can be applied locally make the iris a formidable instrument for these investigations, combining the advantages of in vitro with in vivo methodologies. However, the size of the pupil is determined by antagonistic actions of sympathetic and parasympathetic nerves. This may make interpretation difficult because sympatholytic and parasympathomimetic effects, for example, are phenomenologically identical.

Atropa belladonna is classically known to contain mydriatic potency, ascribed to its anticholinergic activity. However, atropine may possess noncholinolytic activity as well. Atropine and its analogues are known to prevent reuptake of dopamine in the striatum.\(^2\) A similar effect on noradrenaline in the eye could result in mydriasis by a mechanism similar to that of cocaine. The structural similarity of cocaine and atropine has been mentioned before.\(^6\)

In the present paper we have demonstrated a noncholinolytic mydriatic action of atropine, using an exceptional subject whose only neuroeffector mechanism activating the pupil is apparently sympathetic.

Subject, materials, and methods. We\(^6\) have recently described an usual case of Waardenburg syndrome\(^8\)\(^-\)\(^10\) associated with anisocoria and a fixed dilated pupil of the lighter eye. Pharmacologic investigations revealed no abnormality in response to sympathetic agents (phenylephrine, hydroxyamphetamine, guanethidine, and cocaine). On the other hand, no response could be elicited even to high concentrations of cholinomimetic drugs (pilocarpine and phospholine iodide). The results were interpreted to mean that in this patient the sphincter pupillae either does not exist or cannot react to cholinergic transmission. Thus we were provided with an in vivo isolated peripheral sympathetic system free of cholinergic interference.

The autonomic activity in the pupils was estimated by measuring the pupillary diameters in the presence of different drugs, given as eye drops. The following drugs were used: atropine (0.06 percent), homatropine (0.25 percent), cocaine (4 percent), and guanethidine (1 percent). All drugs were given in a dose of 50 \(\mu\)l into each conjunctival sac, except for guanethidine which was administered in a 250 \(\mu\)l dose over 10 minutes. Pupillary responses to cocaine, atropine, and homatropine were measured for 1 hour and those to guanethidine after 4 hours. Each drug was instilled simultaneously into both eyes, and the reactions on the two sides were compared. The tests were performed 1 week apart, with a background illumination of 200 Lx. Pupillary diameter was measured through comparison with a commercial set of black circles while the subject focused at the distance. The activity of the drug was estimated as the mydriatic ratio (M.R.), defined as follows:

\[
\text{M.R.} = \frac{\text{Diameter of pupil after drug application}}{\text{Resting diameter of the pupil}}
\]

For guanethidine, the reciprocal was used.

Results. Both pupils dilated in reaction to atropine. Although the right pupil initially had, and reached, a final greater diameter, the smaller left one increased in size by a larger fraction (Table I). Following guanethidine the pupillary diameters on both sides were diminished by the same fraction (1.2). When cocaine was instilled at the time of maximal response to guanethidine, no intrinsic sympathetic activity could be demonstrated, but atropine and homatropine retained their activity to the same degree as without guanethidine (Table II).

Discussion. We have demonstrated that in the abnormal eye of the subject, atropine and homatropine still retain part of their mydriatic activity. This pupillary dilatation is not likely to depend upon anticholinergic action, since the pupil-size mechanism in this patient is indifferent to pilocarpine and phospholine iodide.\(^9\) The structural similarity between atropine and cocaine\(^6\) and the fact that atropine blocks the reuptake of dopamine\(^7\) have led us to examine the possibility that mydriatic activity of atropine in this case depends upon prevention of reuptake of norepinephrine. For this purpose we have produced


Table I. Pupillary diameters (mm.) and mydriatic ratios (M.R.) in response to 0.06% atropine and 0.25% homatropine.

<table>
<thead>
<tr>
<th></th>
<th>Resting diameter (mm.)</th>
<th>Light response (200 Lx)</th>
<th>Atropine 0.06%</th>
<th>Homatropine 0.25%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diam. (mm.) M.R. Diam. (mm.) M.R.</td>
<td>Diam. (mm.) M.R. Diam. (mm.) M.R.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>7.0 Nil</td>
<td>9.0 1.3</td>
<td>8.5 1.2</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>3.0 Normal</td>
<td>8.5 2.8</td>
<td>8.0 2.7</td>
<td></td>
</tr>
</tbody>
</table>

Table II. The response of guanethidinized pupils to 4% cocaine and 0.06% atropine in terms of pupillary diameter (mm.) and mydriatic ratios (M.R.).

<table>
<thead>
<tr>
<th></th>
<th>Resting diameter (mm.)</th>
<th>Cocaine 4% Diam. (mm.) M.R.</th>
<th>Atropine 0.06% Diam. (mm.) M.R.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>6.0 6.0</td>
<td>7.5 1.3</td>
<td>7.0 2.8</td>
</tr>
<tr>
<td>Left</td>
<td>2.5 2.5</td>
<td>7.0 1.0</td>
<td>7.0 2.8</td>
</tr>
</tbody>
</table>

pharmacologically a transient Horner syndrome, through application of guanethidine. Following guanethidine the mydriatic effect of cocaine was abolished, but not that of atropine or homatropine. Thus, mydriasis must occur through another mechanism, probably a direct action on the radial smooth muscle.

A noncholinergic, nonadrenergic stimulant action of atropine on smooth muscle has been described before. By means of in vitro techniques, contractions by atropine were demonstrated in the esophagus as well as ureteral smooth muscle. However, in organs having antagonistic sympathetic-parasympathetic innervation, these effects are difficult to interpret. It is the congenital abnormality in our patient with Waardenburg syndrome, pupil, parasympathetic innervation.

The relative contribution of this mode of activity of atropine and homatropine in the overall mydriasis produced by these drugs in the normal eye is not likely to be large. It is, moreover, possible that the effect occurs not only in the radial but also in the circular smooth muscle and that these effects antagonize each other. However, the assumption that the mydriatic effect of atropine and homatropine is only a manifestation of the antimuscarinic effects of these drugs is probably an oversimplification.

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REFERENCES