Human Dynamic Closed-Loop Accommodation Augmented by Sympathetic Inhibition

Helena M. Culhane, Barry Winn, and Bernard Gilmartin

PURPOSE. A ciliary $\alpha$-adrenoceptor accommodative effect has been proposed, caused by a small population of $\alpha_1$-inhibitory receptors in excised human ciliary muscle. This study was intended to investigate the effect on the closed-loop dynamic accommodative process of modulating $\alpha_1$-adrenoceptor activity by topical instillation of the $\alpha_1$-adrenergic agonist, phenylephrine hydrochloride.

METHODS. A group of 10 visually normal subjects viewed a photopic (30 candelas/m²) high-contrast Maltese cross, which was modulated sinusoidally (0.05–0.6 Hz) and stepwise over a 2-D range (2–4 D). Monocular temporal accommodation responses were measured using a continuously recording dynamic tracking infrared optometer under two trial conditions: after instillation of saline control solution and 50 minutes subsequent to the instillation of 0.27 μl 0.4% benoxinate hydrochloride and 0.27 μl 2.5% phenylephrine hydrochloride. Pupil size and accommodative amplitude were measured at 90-second intervals for 50 minutes after drug instillation. All accommodative measurements were recorded through a fixed 4-mm pupil.

RESULTS. A significant reduction in accommodative amplitude (11%; $P < 0.05$) was recorded, whereas pupil size showed a significant increase (33%; $P < 0.05$). No significant change in step-response dynamics was observed. However, phenylephrine hydrochloride caused a significant increase in accommodative gain in the low and midtemporal frequency ranges compared with the effect of a saline control treatment. No significant variation in phase lag was observed.

CONCLUSIONS. For the first time in humans, this study shows that augmentation of the $\alpha_1$-inhibitory sympathetic contribution results in increased accommodative gain at low and midtemporal frequencies, which is consistent with findings in animal studies. (Invest Ophthalmol Vis Sci. 1999;40:1137-1143)

The task of maintaining clear vision across a range of viewing distances is achieved by the process of ocular accommodation. The control of accommodation is mediated primarily by parasympathetic input to ciliary smooth muscle resulting in changes in the dioptric power of the crystalline lens in the young eye. In addition, anatomic, physiological, and pharmacologic (in vitro and in vivo) evidence exists supporting sympathetic innervation of ciliary muscle in the young eye. In addition, anatomic, physiological, and pharmacologic (in vitro and in vivo) evidence exists supporting sympathetic innervation of ciliary muscle. Despite preliminary work on the role of the sympathetic division in the control of the dynamic accommodative process in humans, its function remains unclear.

Gilmartin's comprehensive reviews of sympathetic innervation to ciliary muscle and autonomic correlates of nearvision in emmetropia and myopia present evidence in support of a specific sympathetic component in accommodation control. Sympathetic effects are mediated through noradrenaline acting on two sub-classes of postsynaptic receptor classified as $\alpha$ and $\beta$ adrenoceptors. The presence of primarily $\beta_2$-adrenoceptors has been shown in a number of in vitro studies of sympathetic input to human ciliary muscle. The ciliary processes contain approximately 30% of the total number of $\beta_2$ receptors in human iris-ciliary preparations.

The influence of sympathetic innervation, through $\beta$-adrenoceptors in ciliary smooth muscle on open- and closed-loop accommodation has been shown previously by several investigators. For low frequency modulations in stimulus distance (simulating sustained accommodation) under closed-loop conditions, $\beta_2$ antagonism has been found to be sufficient to degrade the optimum balance between the parasympathetic and the sympathetic divisions of the autonomic control system. This provides evidence to show that relatively high levels of sustained accommodation are conducive to the demonstration of $\beta_2$-mediated inhibition of ciliary smooth muscle.

In general, $\alpha_1$- and $\alpha_2$-adrenoceptors are located in postganglionic and preganglionic sites, respectively. The $\alpha_2$-receptors are located on prejunctional membranes and have a role in regulating the release of noradrenaline through inhibition of presynaptic feedback. Pharmacologic research on strips of ciliary muscle in vitro has identified a small population of $\alpha_1$-inhibitory receptors in excised human ciliary muscle, thus showing the potential for a specific ciliary $\alpha$-adrenoceptor effect.

Studies in monkeys and humans have shown that the characteristic features of sympathetic input to the ciliary body are the following: It is inhibitory, it is small (no more than $-2$ D), and it has a relatively slow time course (approximately 10 to 40

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Few investigators have studied the sympathetic dynamic accommodative characteristics in humans, and there is no known study on the effect of a-adrenoceptor on the closed-loop dynamic accommodation process. The a, adrenoceptor agonist phenylephrine hydrochloride has been used to investigate the effect of a, adrenoceptor stimulation on amplitude of accommodation and pupil size. The resultant mydriasis and small but significant reduction in accommodative amplitude have been well documented. In a recent attempt to clarify the functional role of adrenoceptors in accommodative control, phenylephrine hydrochloride (5%) was found to have no effect on tonic accommodation or accommodative adaptation. However, the quasi-static accommodative measurement technique used provides only limited insight into the neurologic control of accommodation under normal closed-loop viewing conditions.

Characteristics of dynamic ocular accommodation (latency, reaction time, velocity, and transfer function), in response to step or sinusoidal change in stimulus vergence (apparent or real stimulus distance), have been investigated by some researchers. Modulation of the temporal aspects of stimulus presentation allows individual innervational components of the accommodation response to be isolated. The purpose of this study was to identify the action of a, adrenoceptors on the closed-loop accommodation response. The effect on accommodative amplitude and pupil size was also investigated.

**METHODS**

Ten visually normal subjects (5 men, 5 women) participated in the study. Subjects ranged in age from 20 to 28 years (mean age, 24.9 ± 2.9 years) and had an average accommodative amplitude of 8.25 ± 1.8 D. A restricted age range was used to minimize the intersubject effect of topical drug pharmacokinetics on the ocular surface. All subjects had light-colored irises, corresponding to standards A to C on the Seddon grading system. Participants had no adverse ocular disorders and no systemic health conditions that contraindicated the use of a-adrenergic drugs. The use of concurrent systemic medication and the recent use of topical ocular decongestants containing phenylephrine or similar drugs (naphazoline or xylometazoline) were also contraindicated. Informed consent was obtained from all subjects after explanation of the nature of the study. All experimental procedures conformed to the recommendations specified in the Declaration of Helsinki.

Monocular (right eye) temporal accommodation responses were measured objectively using a continuously recording dynamic tracking infrared optometer (Fourward Optical Technologies, San Marcos, TX). The instrument tracks the horizontal and vertical position of the first Purkinje image to ensure that the optometer remains on axis during accommodation measurements. Recordings of accommodation can be made that are free of eye movement artifacts over a range of ±5°. The optometer has a resolution of 0.1 D and is based on the Scheiner principle. The analog output from the optometer was fed into a digital storage oscilloscope (model 1604; Gould) that was connected to an on-line computer through an interface (IEEE-488).

A three-dimensional visual stimulus deflector system was used to change optically the vergence (apparent distance) of the accommodation stimulus. This Badal stimulus optometer allowed stimulus vergence to be modulated without changing stimulus size, position, or luminance by movement of a telecentric lens in the optical path. The lens was controlled by a frequency generator that could be used to input square and sine waves at a range of amplitudes and temporal frequencies. A 4-mm artificial pupil was imaged in the subject's natural entrance pupil to remove any variation in performance caused by changes in depth of focus. Subjects viewed monocularly (right eye) a high-contrast photopic (30 candela/m²) Maltese cross target through the Badal stimulus optometer. They were instructed to fixate on the intersection of the cross and to keep the stimulus clear during the experimental trials.

The dynamics of the accommodative response to sinusoidal (0.05, 0.1, 0.2, 0.3, 0.4, and 0.6Hz) and stepwise (0.05Hz) modulations in target vergence over a 2- to 4-D range were investigated before and after (approximately 55 minutes) the instillation by micropipette of 1 drop of 0.4% benoxinate hydrochloride and 1 drop of 2.5% phenylephrine hydrochloride into the lower fornix. Drops contained 27 μl of agent. This procedure has been shown to have little effect on the basic form of the accommodative microfluctuations, determined using power spectrum analysis. The presentation order of the sinusoidal frequency modulations was randomized, because anticipation in the form of phase lead has been recorded. saline-saline control treatments were administered to allow identification of artifacts in the data caused by learning effects.

Continuous recording of accommodation was performed at a sampling rate of 102.4 Hz. A power spectrum was calculated for each trace with a frequency resolution of 0.1 Hz. The probability density function for any one frequency bin (each width 0.1 Hz) in a power spectrum obtained by a single Fourier transform is that of a χ² distribution of order 2. The SD of such a distribution is equal to the mean. By averaging power spectra the confidence in the distribution increases, and the SD correspondingly decreases and becomes equal to $\sqrt{(2/(2m))} \times$ mean value in each frequency bin (where m is the number of spectra). Individual power spectra from each recording, for a given stimulus condition, were integrated to provide a final power spectrum with 60 degrees of freedom. Gain was calculated from the power present at the appropriate frequency in the averaged spectrum.

The effect of the drugs on amplitude of accommodation and pupil size was also monitored. Amplitude of accommodation was assessed subjectively (right eye) with a near-point rule using the standard push-up technique. This clinical measurement of amplitude of accommodation includes the true, total available dioptric change in power and the ocular depth of focus. Therefore, all accommodation measurements were recorded through a fixed 4-mm artificial pupil to standardize the depth-of-field for each subject and to minimize aberrations from a widely dilated pupil. Pupil size was determined using a traditional infrared technique as explained by other investigators.
RESULTS

Accommodative Amplitude and Pupil Size

Initial measures of amplitude of accommodation and pupil size were normalized to 100% and 0%, respectively. Subsequent measures of these parameters were referred to these initial values. Group averaged changes in accommodative amplitude and pupil size after the instillation of the topical agent are shown in Figure 1. An analysis of variance (ANOVA) showed a significant ($P < 0.05$) reduction in accommodative amplitude (mean ± SEM; 11.22% ± 2.76%; 0.93 ± 0.23 D), and a significant increase ($P < 0.05$), in pupil size (33.04% ± 3.16%; 1.9 ± 0.32 mm) after 50 minutes.

Accommodative Responses to Sinusoidal Modulations

It is apparent from the raw data in Figure 2 (frequency modulation 0.3 Hz), that the naturally occurring microfluctuations in accommodation make it difficult to judge accurately the magnitude of the accommodation response. Fourier analysis was therefore used to quantify the accommodative responses for each trial and bode plots (semi-log plots of sinusoidal temporal frequency against gain) were calculated. Gain represents the ratio of the mean accommodative output magnitude to the input magnitude.

The group averaged bode plots under the saline and treatment conditions are shown in Figure 3. A two-factor repeated-measure ANOVA showed a significant increase in accommodative gain after the instillation of phenylephrine HCl 2.5%. Post hoc comparisons were performed that showed a low-pass bias (Scheffé test: 0.05 Hz, $P = 0.036$; 0.1 Hz, $P = 0.0005$; 0.2 Hz,
FIGURE 3. Average bode plots of accommodative gain (±SEM) under both test conditions: saline (●) and 2.5% phenylephrine hydrochloride (○).

\[ P = 0.000018 \text{, and } 0.3 \text{ Hz, } P = 0.003 \]  
An analysis of the phase relationship (Fig. 4) showed no significant difference between the saline and 2.5% phenylephrine hydrochloride conditions (ANOVA, \( P > 0.05 \)).

To eliminate artifacts associated with voluntary influences (e.g., anticipation), learning effects, and nonoptical influences, saline-saline control trials were undertaken. The results showed no significant difference in accommodative gain or phase lag (ANOVA, \( P > 0.05 \)) when measurements were repeated under identical experimental conditions.

**Accommodative Responses to Stepwise Modulations**

The accommodation response was recorded while the stimulus was modulated using a 0.05-Hz square-wave input over two vergence ranges (2-4 D and 3-4 D) before and after each treatment. A single-factor ANOVA showed no significant change (\( P > 0.05 \)) in step response times after instillation of the drug. Average response times are shown in Table 1.

**DISCUSSION**

The results of the present study in human eyes are consistent with observations from animal studies that have shown a sympathetic component to the accommodation control mechanism.\(^4\)\(^4\)\(^2\) We have shown that after the instillation of the \( \alpha_2 \)-adrenoceptor agonist, a significant increase in accommodative gain at low and midtemporal frequencies was induced, although no significant difference in phase lag was detected. The increased accommodative gain could not be accounted for solely by voluntary or learning effects, because no significant difference in gain was detected in the saline-saline control trials.

An optimum balance between the parasympathetic and sympathetic control of accommodation is necessary to respond to temporal variations in target distance and to prevent adaptation after sustained near vision. The results show that additional stimulation of the postsynaptic \( \alpha_2 \)-inhibitory receptors with 2.5% phenylephrine hydrochloride allowed the accommodative system to track more accurately at low and midtemporal frequencies. Response enhancement in the direction of decreasing accommodation would be in accord with the inhibitory (negative accommodation) role outlined in animal studies of sympathetic innervation to the ciliary body.\(^4\)\(^4\)\(^2\) A hyperopic (negative) shift in accommodation has been shown in 13 young adult monkeys after electrical stimulation of the superior cervical sympathetic ganglion.\(^4\) However, there was no consideration of any \( \alpha_2 \)-inhibitory ciliary smooth muscle effects. Further evidence from animal studies in support of a sympathetic component to the accommodation response is the recent report of a myopic (positive) shift of approximately 0.57 D in the baseline refractive error after superior cervical ganglionectomy in monkeys.\(^4\)

Phenylephrine optimizes the accommodation response profile that is indicated by the low-pass characteristics of the bode plots. At high temporal frequencies the reflex element of the system predominates, and therefore stimulation of the sympathetic input does not result in increased responsiveness. The result suggests that the sympathetic component of the response is necessary to provide maximum negative accommodation.

The selection of phenylephrine was a consequence of the ethical constraints on agents and procedures that can be used for in vivo work in humans. Although phenylephrine is highly specific for \( \alpha_1 \) receptors,\(^4\) it is well tolerated, and has ocular effects that have been well documented, it is acknowledged that the major receptor subtypes are complemented by a variety of additional subtypes and further, that autonomic nerves release more than one transmitter that may subsequently combine to produce systems for chemical coding.\(^4\)

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TABLE 1. Average Response Times After Drug and Control Treatments

<table>
<thead>
<tr>
<th>Step Magnitude (D)</th>
<th>2-4</th>
<th>4-2</th>
<th>3-4</th>
<th>4-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>0.87 ± 0.34</td>
<td>0.72 ± 0.11</td>
<td>0.82 ± 0.46</td>
<td>0.74 ± 0.23</td>
</tr>
<tr>
<td>Phenylephrine HCl</td>
<td>0.82 ± 0.27</td>
<td>0.85 ± 0.14</td>
<td>0.78 ± 0.26</td>
<td>0.85 ± 0.16</td>
</tr>
</tbody>
</table>

Values are mean ± SEM, expressed in seconds.

has to be taken of the cross-linkage that can occur between cholinergic and adrenergic transmitters and receptors at pre-synaptic and postsynaptic sites. The interactions create a complex mechanism for modulation of transmitter release that is not yet fully understood.44-48

A significant feature of the animal study by Tornqvist4 investigating autonomic control of accommodation was the selection of appropriate temporal frequencies for stimulation of the system that were matched to the physiological role of sympathetic innervation to the ciliary muscle. This rationale has been adopted in the present study in humans in an attempt to isolate the subsystems of neurologic control. Stimulus parameters were thus selected to show the susceptibility of the accommodative response at specific temporal frequencies to drug-induced receptor effects that modulate the normal equilibrium between the autonomic components.

The effect on intraocular vasculature of instilling an α-adrenoceptor agonist has also been considered. Tornqvist4 used α-adrenoceptor antagonists to minimize the vasoconstrictive effects of sympathetic stimulation. However, this failed to inhibit the hyperopic shift in refraction reported. It therefore seemed that the hyperopic shift was independent of vascular changes and was solely associated with lenticular changes caused by direct innervation of the ciliary muscle. Intraocular vasculature effects were thus considered minimal.

The partitioning of vascular and specific smooth muscle receptor responses to phenylephrine is not feasible when measuring in vivo responses. Although this restriction somewhat confounds conclusions concerning receptor-mediated accommodative responses, the absence of effect of phenylephrine on tonic resting levels of accommodation,49-51 compared with the significant reduction evident for amplitude of accommodation,25,49,52 suggests some augmentation of α-receptor-mediated response similar to that reported for β-receptor antagonists.18

The reduction of accommodative amplitude after the instillation of 2.5% phenylephrine hydrochloride is also consistent with previous findings.22,25 It has been suggested that this inhibition may be partly artifactual, caused by the enlargement of the pupil,24 which decreases the optical depth-of-focus. Unlike findings in previous studies, our recordings reflect the true influence of phenylephrine hydrochloride on accommodative amplitude, because a constant artificial pupil diameter was used. The maximum reduction in accommodative amplitude with phenylephrine hydrochloride reported in these studies was approximately 2.5 D, when measurements were taken through the naturally dilated pupil. The close relationship between this and the maximum inhibitory sympathetic response from superior cervical ganglion stimulation of approximately 2 D was noted.5 We propose therefore that the effect we were recording may have been the negative shift in accommodation and not solely a vasoconstrictive vascular effect, as previously thought.

The significant change in pupil size detected is also consistent with that in previous publications.23,53 An average mydriasis of 2 mm in 50 minutes (no topical anesthetic was used) has been reported,23 which is consistent with the current findings of a 1.9-mm mydriasis over the same period. Thus, the reputed increased mydriasis subsequent to the instillation of a topical anesthetic53 (0.4% benoxinate hydrochloride) is not apparent from our findings.

We propose that in relation to the profile of autonomic innervation, the ocular accommodative system exhibits frequency-dependent characteristics. Responses to higher temporal frequency modulations and step modulations of stimulus vergence are regulated by the faster parasympathetic system, which dominates the control of closed-loop dynamic ocular accommodation. However, at lower temporal frequencies, the conditions are favorable for the slower inhibitory sympathetic system to contribute more to the optimum aggregate response. This may be appreciated from the low-pass enhancement observed after the drug instillation. The increase in response magnitude may result from the selective stimulation of elements within the aggregate accommodation response that have a slow time course.

We present evidence supporting a significant role for the α1-adrenoceptor element of sympathetic innervation in ocular accommodation. Consideration of the dominant parasympathetic input and the time-dependent sympathetic component is therefore necessary when constructing models of accommodation control.

Such models invariably incorporate the integration of vergence and accommodation components54,55 and in this regard the work of Demer et al.56 is of interest. Based on histochemical and immunohistochemical studies in human cadaveric and monkey orbits, they propose a smooth muscle system of eye movement control that is complementary to that based on striated muscle. The system modulates eye movements through a peribulbar distribution of smooth muscle cells that receive parasympathetic and sympathetic inputs from the autonomic nervous system. Although the specific nature of this modulation has yet to be elucidated, the finding supports the idea that the autonomic nervous system may have a general regulatory role in maintaining appropriate responses to sustained near vision.

References


