Human Dynamic Closed-Loop Accommodation Augmented by Sympathetic Inhibition

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PURPOSE. A ciliary α-adrenergic receptor accommodative effect has been proposed, caused by a small population of α₁-inhibitory receptors in excised human ciliary muscle. This study was intended to investigate the effect on the closed-loop dynamic accommodative process of modulating α₁-adrenergic activity by topical instillation of the α₁-adrenergic agonist, phenylephrine hydrochloride.

METHODS. A group of 10 visually normal subjects viewed a photopic (30 candela/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 α₁-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 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 near-vision in emmetropia and myopia present evidence in support of a specific sympathetic component in accommodation control. Sympathetic effects are mediated through noradrenergic acting on two sub-classes of postsynaptic receptor classified as α and β adrenoceptors. The presence of primarily β₂-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 β₂ receptors in human iris-ciliary preparations.

The influence of sympathetic innervation, through β₂-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, β₂ antagonism has been found to be sufficient to degrade the optimum balance between the parasympathetic and the sympathetic divisions of the autonomic control systems. This provides evidence to show that relatively high levels of sustained accommodation are conducive to the demonstration of β₂-mediated inhibition of ciliary smooth muscle.

In general, α₁- and α₂-adrenoceptors are located in postganglionic and preganglionic sites, respectively. The α₂ 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 α₁-inhibitory receptors in excised human ciliary muscle, thus showing the potential for a specific ciliary α₁-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), it has a relatively slow time course (approximately 10 to 40
ffects on accommodative amplitude and pupil size was also
purpose of this study was to identify the action of α-adreno-
some researchers. Modulation of the temporal aspects of
viewing conditions.

Ten visually normal subjects (5 men, 5 women) participated in
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 pharmacoki-
etics on the ocular surface. All subjects had light-colored
irises, corresponding to standards A to C on the Seddon grad-
ing system. Participants had no adverse ocular disorders and
no systemic health conditions that contraindicated the use of
α-adrenergic drugs. The use of concurrent systemic medication
and the recent use of topical ocular decongestants containing
phenylephrine or similar drugs (naphazoline or xylometazo-
line) were also contraindicated. Informed consent was ob-
tained from all subjects after explanation of the nature of the
study. All experimental procedures conformed to the recom-
mendations specified in the Declaration of Helsinki.

Monocular (right eye) temporal accommodation re-
sponses were measured objectively using a continuously re-
cording dynamic tracking infrared optometer (Fourward Opti-
cal 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 accommo-
dation 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 optome-
ter 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 tele-
centric 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 sinusoi-
dal (0.05, 0.1, 0.2, 0.3, 0.4, and 0.6 Hz) and stepwise (0.05 Hz)
modulations in target vergence over a 2- to 4-D range were
investigated before and after (approximately 55 minutes after
the instillation by micropipette of 1 drop of 0.4% benoxinate hy-
drochloride 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 us-
ing power spectrum analysis. The presentation order of the
sinusoidal frequency modulations was randomized, be-
cause anticipation in the form of phase lead has been re-
corded. 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 calcu-
lated for each trace with a frequency resolution of 0.1 Hz. The
probability density function for any one frequency bin (each
of 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 corre-
spondingly decreases and becomes equal to √(2/2m) × mean
value in each frequency bin (where m is the number of spec-
tra). 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 calcu-
lated from the power present at the appropriate fre-
quency in the averaged spectrum.

The effect of the drugs on amplitude of accommodation
and pupil size was also monitored. Amplitude of accommo-
dation was assessed subjectively (right eye) with a near-point rule
using the standard push-up technique. This clinical mea-
surement 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
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 = 0.00005; 0.2 Hz,
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.\(^7\)\(^\text{,}^{-42}\) We have shown that after the instillation of the $\alpha_1$-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.\(^4\)\(^\text{,}^{-42}\) A hyperopic (negative) shift in accommodation has been shown in 13 young adult monkeys after electrical stimulation of the superior cervical sympathetic ganglion.\(^\text{,}^{-4}\) However, there was no consideration of any $\alpha_1$-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.\(^4\) Account also

\[ P = 0.000018, \text{ and } 0.3 \text{ Hz}, P = 0.003 \]. 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.

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has to be taken of the cross-linkage that can occur between cholinergic and adrenergic transmitters and receptors at presynaptic 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 Törnqvist4 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 intracocular vasculature of instilling an α-adrenoceptor agonist has also been considered. Törnqvist4 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. Intracocular 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 partially artifactual, caused by the enlargement of the pupil,24 which decreases the ocular 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


