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Adrenoceptors Affect Accommodation by Modulating Cholinergic Activity

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Abstract: In an attempt to clarify the functional role of adrenoceptors in accommodation, the effects of various adrenergic agents on the state of accommodation were studied. Fifty-two emmetropic, visually normal subjects (24.6 ± 0.42 years old) participated in this study. Using an infrared optometer, the far and near points of accommodation were measured by a quasistatic method. Tonic accommodation and accommodative adaptation were also investigated. All these parameters were measured before and after topical application of various adrenergic agents. Both bunazosin hydrochloride (0.1%) and phenylephrine hydrochloride (5%) had no effect on tonic accommodation and accommodative adaptation. However, bunazosin hydrochloride increased the near point of accommodation. Timolol maleate (0.5%) and isoproterenol hydrochloride (3.0%) did not affect tonic accommodation. Isoproterenol hydrochloride evoked a hyperopic shift of the far point of accommodation by 0.23 ± 0.42 diopters (D). Additionally, accommodative adaptation was increased by timolol maleate (0.36 ± 0.62 D) and decreased by isoproterenol hydrochloride (0.18 ± 0.48 D). These results indicate that both α and β adrenoceptors affect accommodation. Activation of α adrenoceptors increased the near point of accommodation and activation of β adrenoceptors decreased accommodative adaptation, which suggests that activation of adrenoceptors may modify parasympathetic activity; hence, affecting the state of accommodation. **Jpn J Ophthalmol 1998;42:66–70** © 1998 Japanese Ophthalmological Society

Key Words: Accommodation, adrenoceptors, isoproterenol, timolol, sympathetic innervation.

Introduction

Numerous studies[1–7] have reported the effect of sympathetic innervation or sympathomimetic drugs on the state of accommodation since Morat and Doyon[8] first showed the hyperopic shift after stimulation of the sympathetic nerve in dogs. Histological investigation revealed the presence of adrenergic nerve fibers in the ciliary muscle.[9] Physiological investigation[10,11] also suggested the presence of adrenergic receptors in the ciliary muscle in various species, including humans. It is now, thus, generally accepted that the sympathetic nervous system has some effect on accommodation. However, the nature of the control mechanisms by which the sympathetic system affects accommodation has not been clarified. Toates[12] proposed the dual innervation model: that the resting position is determined by the equilibrium established between the tonus levels of the sympathetic and the parasympathetic nervous systems. Gilmartin and Hogan,[2] and Gilmartin[3] suggested that the rapid changes in accommodative response that are required for normal visual tasks are solely controlled by parasympathetic nerves, whereas sustained visual tasks involve both parasympathetic and sympathetic nervous systems. Furthermore, it is also evident that the level of accommodation is changed by previous accommodative stimuli.[13] In an attempt to clarify the functional role of adrenergic receptors in accommodation, especially the changes in accommodation following a near task, the effects of various adrenergic agents on accommodation were studied.

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Materials and Methods

Subjects

After an explanation of the purpose and procedures of the study, written informed consent was given by all subjects. This research followed the tenets of the Declaration of Helsinki. Fifty-two visually normal male and female subjects 19–28 years of age (mean: 24.6 ± 2.7 years) participated in this study. Each subject underwent medical and ophthalmic examinations 7–14 days before the study. Subjects had refraction (spherical equivalent) between −2.0 diopters (D) and +0.5 D and astigmatism less than 0.75 D.

Apparatus

Static characteristics of the accommodative function are often displayed on a graph where the abscissa is accommodative stimulus (AS) and the ordinate is accommodative response (AR). We have developed[14] a method of quasistatic recording that makes rapid recording of the AS/AR relationship possible. While AS is slowly being increased from −12.5 D to +12.5 D and slowly being decreased from +12.5 D to −12.5 D with a constant velocity (0.2 D/S), AR is measured continuously using an infrared optometer that is a modification of a commercially available automated refractometer (Nidek AR-2000, Gamagouri). Accommodative stimulus and AR are recorded on the abscissa and the ordinate of an x–y recorder, respectively, as shown in Figure 1. Target velocity is set at 0.2 D/S to avoid dynamic delay of accommodation. Using this velocity, it takes 250 seconds for one complete measurement cycle.

Emmetropic subjects can respond in the second and the third quarters of measurement (see Figure 1, which was obtained in a slightly myopic subject). Accommodative stimulus and AR are simply expressed in dioptric distance from the eye to the stimulus position and to the point where the eye focuses, respectively.

Ametropic subjects did not wear correction lenses and thus the AR plots were shifted along the AR–AS line. Far and near points of accommodation were determined from the upper and lower plateaus of the trace. Tonic accommodation (empty field accommodation) was determined by measuring the accommodation level in the region where vision was fogged substantially (i.e., 6 D farther than the far point). The difference in tonic accommodation between pre- and post-near vision tasks was calculated as accommodative adaptation.

Procedures

Subjects were randomly allocated to five different drug groups. The initial measurement was taken after 15 minutes of dark adaptation. All accommodative parameters were measured before and after topical

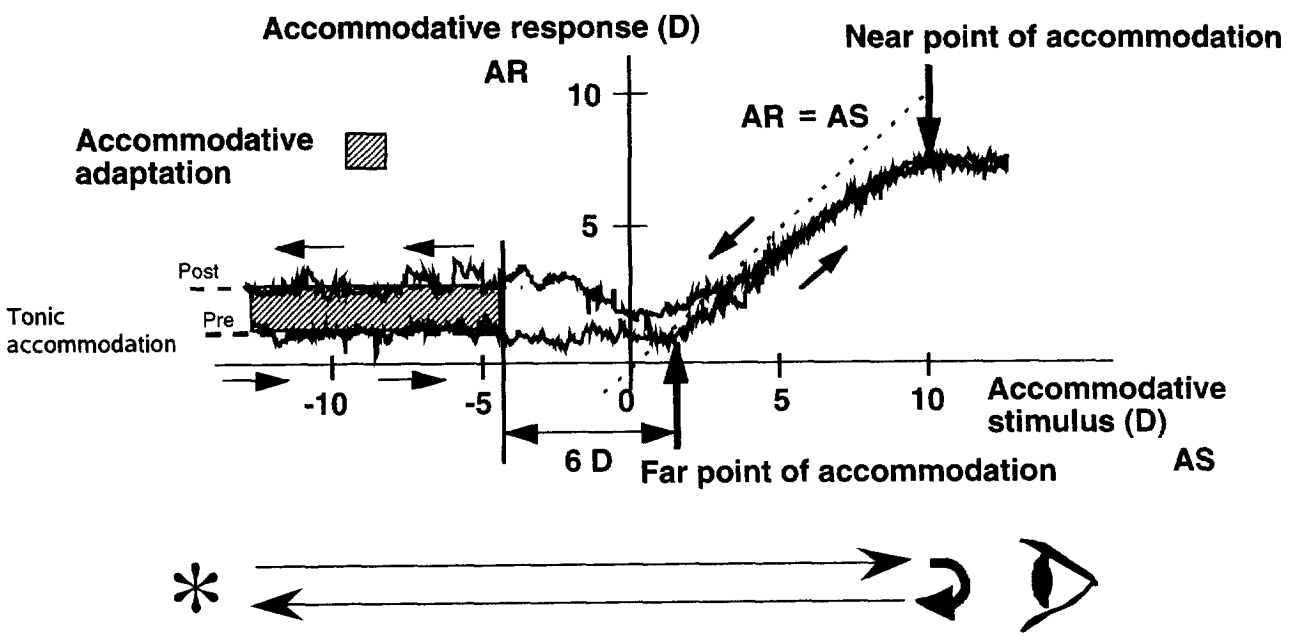

Figure 1. Quasi-static recording of slightly myopic subject.

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instillation of various adrenergic agents: phenylephrine HCl 5.0% (α_1 agonist), bunazosin HCl 0.1% (α_1 antagonist), isoproterenol HCl 3.0% (nonselective β agonist), timolol maleate 0.5% (nonselective β antagonist), and betaxolol HCl 0.5% (β_1 antagonist). Each drug was applied topically and applied again 10 minutes later (50 μl each time). A 15-minute dark adaptation period 1 hour after the last drug instillation was followed by the second measurement of the accommodative parameters (Figure 2).

Results

Timolol maleate and isoproterenol did not affect either the near point of accommodation or tonic accommodation. Accommodative adaptation, however, was increased by timolol maleate (0.36 ± 0.62 D; $P < 0.01$, paired t-test), as shown in Figure 3, and decreased by isoproterenol HCl (0.18 ± 0.48 D; $P < 0.05$, paired t-test). Betaxolol HCl also increased accommodative adaptation (0.12 ± 0.19 D; $P < 0.05$, paired t-test). Isoproterenol HCl evoked a hyperopic shift of the far point of accommodation by 0.23 ± 0.42 D ($P < 0.05$, paired t-test), but neither timolol maleate nor betaxolol HCl affected the far point of accommodation ($P > 0.05$, paired t-test) (Figure 4).

Table 1 and Figure 4 summarize the effects of the various adrenergic agents on the far and near points of accommodation, tonic accommodation, and accommodative adaptation. Neither bunazosin HCl nor phenylephrine HCl had an effect on the far point of accommodation, tonic accommodation, or accommodative adaptation. The near point of accommodation was significantly increased by bunazosin HCl but was unaffected by phenylephrine HCl.

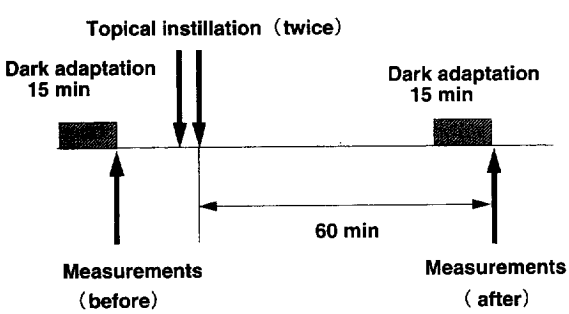

Figure 2. Measurement procedure.

Discussion

α Adrenergic Mechanisms

Our present results indicate that the α adrenergic agents had little effect on tonic accommodation or the far point of accommodation. Rosenfield et al[5] and Garner et al[1] also showed a similar result using phenylephrine HCl. Zetterström[15] reported a myopic shift of the far point of accommodation in daylight and darkness with phenylephrine, although the shift was not observed in the presence of an artificial pupil. It is, thus, reasonable to conclude that the α adrenergic system is not involved in the steady state of accommodation. However, our present results and those of other investigators[1,15,16] show that the α adrenergic agents did affect the amplitude of accommodation. Epinephrine, amphetamine, and phenylephrine, all α agonists, have been shown to decrease the near point of accommodation. Although we were unable to demonstrate phenylephrine's decreasing effect on the near point of accommodation, we showed the increasing effect (0.49 ± 1.09 D) of

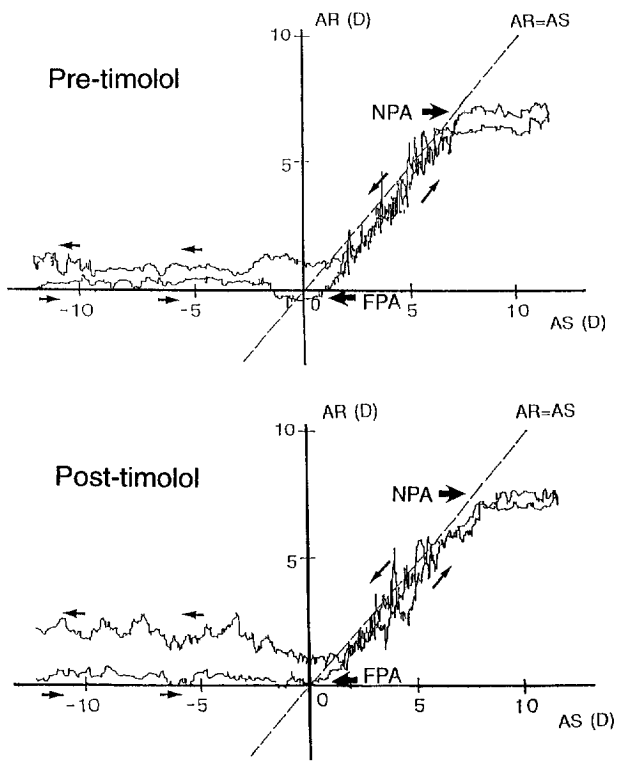

Figure 3. Example of measurements. Accommodative adaptation increased following instillation of timolol maleate while near point of accommodation (NPA) and tonic accommodation were unchanged. FPA represents the far point of accommodation.

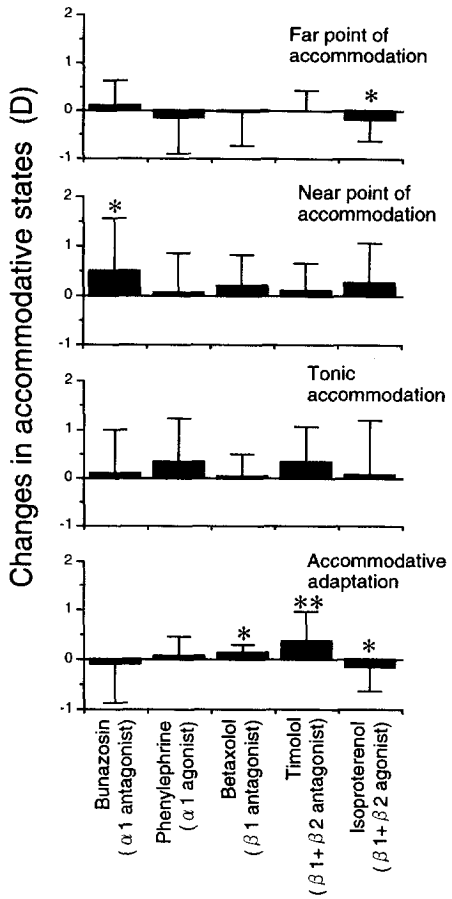

Figure 4. Changes in accommodation following installation of various autonomic agents. Each bar represents 1 SD. $*P < 0.05$. $**P < 0.01$.

bunazosin, an α_1 antagonist, on the near point of accommodation. Zetterström[15] also reported the increase of the near point of accommodation by applying an α_1 antagonist, thymoxamine. We can conclude that the α adrenergic mechanism is involved in the amplitude of accommodation, not in the steady state of accommodation. Yoshitomi and Ito[16] reported that α_2 adrenoceptors exist on the cholinergic nerve terminal of the dog ciliary muscle. When activated, they decreased release of acetylcholine from the nerve terminal and hence decrease the amplitude of contraction. Norepinephrine did not change the resting tension of this muscle because α_1 adrenoceptors did not exist on the muscle. This mechanism in the dog may explain the present results in humans because the α adrenergic agents affect the amplitude of accommodation (i.e., cholinergic activity) without changing the steady state of accommodation.

β Adrenergic Mechanisms

In the present study, β adrenergic agonists or antagonists had no effect on the tonic accommodation or near point of accommodation. However, a hyperopic shift of the far point of accommodation was observed in response to topical isoproterenol HCl without any effect by timolol maleate or betaxolol HCl. Gilmartin and Hogan[2] reported a significant hyperopic shift in tonic accommodation by applying isoprenaline and a myopic shift by applying timolol maleate in a laser optometer experiment. Zetterström[15]

Table 1. Accommodation Measurements (Mean ± SD)

	Far Point of Accommodation (D)	Near Point of Accommodation (D)	Tonic Accommodation (D)	Accommodative Adaptation (D)
Bunazosin HCl (α_1 antagonist)				
Pre	0.85 ± 0.85	8.45 ± 1.32	0.85 ± 0.97	0.71 ± 0.71
Post	0.96 ± 0.81	8.94 ± 1.13[a]	0.95 ± 1.15	0.62 ± 0.71
Phenylephrine HCl (α_1 agonist)				
Pre	0.69 ± 1.00	7.54 ± 1.77	0.90 ± 0.98	0.53 ± 0.62
Post	0.52 ± 0.73	7.62 ± 1.39	1.22 ± 1.24	0.59 ± 0.69
Betaxolol HCl (β_1 antagonist)				
Pre	0.80 ± 1.19	7.78 ± 1.11	0.41 ± 0.61	017 ± 0.31
Post	0.77 ± 0.73	7.98 ± 0.76	0.44 ± 0.47	0.29 ± 0.25[a]
Timolol maleate (β_1 + β_2 antagonist)				
Pre	0.66 ± 0.96	7.09 ± 1.29	0.62 ± 0.88	0.41 ± 0.37
Post	0.67 ± 0.72	7.18 ± 1.10	0.96 ± 1.63	0.77 ± 0.63[b]
Isoproterenol HCl (β_1 + β_2 agonist)				
Pre	0.51 ± 0.51	7.33 ± 1.14	1.19 ± 1.16	0.42 ± 0.53
Post	0.28 ± 0.60*	7.60 ± 0.81	1.24 ± 1.17	0.24 ± 0.31[a]

[a] $P < 0.05$ (paired t-test).
[b] $P < 0.01$ (paired t-test).

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reported similar results, although the hyperopic shift by isoproterenol was not statistically significant. An in vitro study[10] using human ciliary muscle also indicates the presence of β adrenoceptors on this muscle that caused relaxation activation. Thus, we can conclude that the activation of β adrenoceptors, located on the ciliary muscle relaxes this muscle and induces hyperopic shift. However, the hyperopic shift in this study was only 0.23 ± 0.42 D, and timolol maleate and betaxolol HCl had no effect on the far point of accommodation. The physiological importance of the β adrenoceptors may be small.

Accommodative adaptation, the difference in tonic accommodation between baseline and following near task, was decreased by isoproterenol HCl and increased by timolol maleate and betaxolol HCl in our present study. Gilmartin and Bullimore[17] reported that the β antagonist timolol maleate significantly modified the pattern of regression of accommodation after a near vision task. Since we failed to show the effect of timolol maleate or betaxolol HCl on the resting point of accommodation, we believe that β adrenoceptors may play a more important role in modulating parasympathetic activity than in acting directly on the ciliary muscle.

Our present data may suggest that the adrenoceptors affect accommodation mainly by modifying cholinergic activity. Presumably, α adrenoceptors modify the amplitude of accommodation because α adrenoceptors are located on the cholinergic nerve terminal and act to control acetylcholine release from the terminal. Additionally, β adrenoceptors modify the regression of accommodation after a near vision task. It is believed that the adrenergic system affects accommodation by modulating cholinergic activity and not by acting directly on the ciliary muscle.

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