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The effect of topical adrenergic and anticholinergic agents on the choroidal thickness of young healthy adults

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ABSTRACT

The human choroid is capable of rapidly changing its thickness in response to a variety of stimuli. However little is known about the role of the autonomic nervous system in the regulation of the thickness of the choroid. Therefore, we investigated the effect of topical parasympatholytic and sympathomimetic agents upon the choroidal thickness and ocular biometrics of young healthy adult subjects. Fourteen subjects (mean age 27.9 ± 4 years) participated in this randomized, single-masked, placebo-controlled study. Each subject had measurements of choroidal thickness (ChT) and ocular biometrics of their right eye taken before, and then 30 and 60 min following the administration of topical pharmacological agents. Three different drugs: 2% homatropine hydrobromide, 2.5% phenylephrine hydrochloride and a placebo (0.3% hydroxypropyl methylcellulose) were tested in all subjects; each on different days (at the same time of the day) in randomized order. Participants were masked to the pharmacological agent being used at each testing session. The instillation of 2% homatropine resulted in a small but significant increase in subfoveal ChT at 30 and 60 min after drug instillation (mean change 7 ± 3 μm and 14 ± 2 μm respectively; both $p < 0.0001$). The parafoveal choroid also exhibited a similar magnitude, significant increase in thickness with time after 2% homatropine ($p < 0.001$), with a mean change of 7 ± 0.3 μm and 13 ± 1 μm (in the region located 0.5 mm from the fovea center), 6 ± 1 μm and 12.5 ± 1 μm (1 mm from the fovea center) and 6 ± 2 μm and 12 ± 2 μm (1.5 mm from the fovea center) after 30 and 60 min respectively. Axial length decreased significantly 60 min after homatropine ($p < 0.01$). There were also significant changes in lens thickness (LT) and anterior chamber depth (ACD) ($p < 0.05$) associated with homatropine instillation. No significant changes in choroidal thickness, or ocular biometrics were found after 2.5% phenylephrine or placebo at any examination points ($p > 0.05$). In human subjects, significant increases in subfoveal and parafoveal choroidal thickness occurred after administration of 2% homatropine and this implies an involvement of the parasympathetic system in the control of choroidal thickness in humans.

1. Introduction

The choroid is a highly vascularised layer that plays an important role in normal ocular function. It supplies the outer retina with oxygen and nutrients under highly regulated blood flow, acts as a heat diffuser that protects the photoreceptors and also secretes growth factors (Nickla and Wallman, 2010). The choroid also directly modulates the intraocular pressure (IOP) via vasomotor control of blood flow and indirectly through its role in uveoscleral outflow. Given the vascular nature of the tissue, the choroid's morphology is mainly determined by the course and branching pattern of the ciliary arteries (Bill et al., 1983). It also contains non-vascular smooth muscle cells, a network of spindle- or star-shaped cells that are thought to play a role in altering the thickness of the choroid under the influence of local mediators and intrinsic choroidal neurons that receive input from the sympathetic and parasympathetic nervous system (Nickla and Wallman, 2010; Lütjen-Drecoll, 2006).

Advances in spectral domain optical coherence tomography (SD-OCT) technology have enabled the visualisation and reliable measurements of the human choroid (Ikuno et al., 2010; Hirata et al., 2011; Ouyang et al., 2011). Estimates of the average subfoveal choroidal thickness in the healthy eyes of adult populations (age 18 and over) have ranged between 192 and 354 μm dependent upon the age and refractive error distribution of the population

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(Ikuno et al., 2010; Hirata et al., 2011; Ouyang et al., 2011). Some topographical variations in the choroidal thickness across the posterior pole have also been found, with the choroid consistently reported to be thicker superiorly and temporally, compared to nasal and inferior regions (Hirata et al., 2011; Ouyang et al., 2011). Recent clinical studies have found changes in ChT to be associated with a number of ocular diseases, such as central serous chorioretinopathy (Maruko et al., 2011b), polypoidal choroidal vasculopathy (Koizumi et al., 2011), age related macular degeneration (Manjunath et al., 2011), inflammatory eye diseases (Maruko et al., 2011a), inherited retinal dystrophies (Yeoh et al., 2010), diabetic retinopathy (Esmaeelpour et al., 2011), and glaucoma (Maul et al., 2011). Changes in the thickness of the human choroid have also been found associated with age (Manjunath et al., 2011) and the presence of refractive error (Ikuno et al., 2010; Hirata et al., 2011). Short term changes in human choroidal thickness have also been reported, associated with time of the day (Brown et al., 2009; Chakraborty et al., 2011; Tan et al., 2012), smoking (Sızmaz et al., 2013), caffeine intake (Vural et al., 2014) and with imposed retinal image blur (i.e. hyperopic and myopic defocus) (Read et al., 2010; Chakraborty et al., 2012, 2013).

Additionally, evidence from animal studies suggests that short-term changes in the thickness of the choroid associated with retinal image blur are related to longer term changes in eye growth and the development of refractive errors (Wallman et al., 1995). The magnitude of choroidal thickness variations in relation to defocus found in humans (Read et al., 2010; Chakraborty et al., 2012, 2013) and mammals (Hung et al., 2000) are substantially smaller than those found in avian species (Wallman et al., 1995). Furthermore, several non-selective and selective (M4) muscarinic antagonists have been found to cause a transient thickening of the choroid in chicks (Nickla et al., 2013) or to prevent the choroidal thinning that is normally associated with form-deprivation myopia (McBrien et al., 2011). In contrast, a number of non-specific muscarinic agonists stimulated eye elongation and choroidal thinning in intact chicken eyes (Nickla et al., 2013).

Although the exact mechanism underlying reports of short-term changes in choroidal thickness is not known, previous studies have revealed a rich autonomic vasoactive nerve supply to the choroid involving the activation of sympathetic adrenergic and parasympathetic muscarinic receptors (Neuhuber and Schrödl, 2011). Parasympathetic nerves derived from the pterygopalatine ganglion, via the facial nerve, form a dense perivascular plexus around the choroidal vessels and mediate an increase in blood flow by vasodilatation. These fibres also terminate on non-vascular smooth muscle cells and modulate their tonus (Nickla and Wallman, 2010; Neuhuber and Schrödl, 2011). In addition, the choroid receives innervation from the ciliary ganglion, via the oculomotor nerve that terminates on blood vessels and non-vascular smooth muscle. However, the role of these fibres in the regulation of choroidal blood flow in mammals is not well established, compared to birds where they comprise the main parasympathetic input to the choroid (Nickla and Wallman, 2010; Neuhuber and Schrödl, 2011). A dense sympathetic innervation originates from the ipsilateral superior cervical ganglion, its stimulation causes choroidal vasoconstriction mainly via activation of α_1–adrenergic receptors located in the smooth muscle cells of the vessels (Lanigan et al., 1988). Apart from the autonomic innervation, the choroid also receives the sensory fibres that arise from the trigeminal ganglion via ophthalmic nerve that exert a vasodilatatory influence on choroidal blood flow through local effector function-"axon reflex" in addition to the sensory functions (Nickla and Wallman, 2010; Neuhuber and Schrödl, 2011).

The rich autonomic innervation to various choroidal structures suggests a potential involvement of the autonomic system in the regulation of choroidal thickness, either through modulation of choroidal blood flow, and/or alterations in the tone of non-vascular smooth muscle (Nickla and Wallman, 2010).

We have examined the effects of the modification of the autonomic nervous system activity upon choroidal thickness through the use of topical parasympatholytic and sympathomimetic agents. This was measured with SD-OCT at 30 and 60 min after cholinergic blockade or adrenergic stimulation on different days in healthy young adults. By investigating ocular biometry after topical adrenergic and anticholinergic agent administration, we hoped to improve our understanding of the mechanisms regulating the thickness of the choroid in humans.

2. Material and methods

2.1. Subjects

Fourteen young healthy subjects (mean age 27.9 ± 4 years) participated in this randomized, single-masked, placebo-controlled study. The study and protocol conformed to the tenets of the Declaration of Helsinki and was approved by the university human research ethics committee. Subjects were recruited primarily from the students and staff of the university. Sixty four percent of the participants ($n = 9$) were male and 50% were Caucasian (Caucasian $n = 7$, Indian $= 6$, East Asian $n = 1$). Written informed consent was obtained from participants after thorough explanation of the nature and risks of the experiment before commencement of the study. None of the participants had any significant ocular or systemic disease and had no history of ocular injury or surgery.

Before the study, each participant underwent a full eye examination to determine their refractive status and to ensure they met the criteria of good ocular health. All subjects had normal visual acuity of logMAR 0.00 or better. Their mean spherical equivalent refractive error was −0.62 ± 1.42 DS (range −4.00 to +0.75 DS). The majority of participants exhibited low refractive errors (+0.75 to −0.75 DS) with only 2 subjects with myopic refractive errors > −0.75 DS. No participant exhibited anisometropia of greater than 1.00 DS or cylindrical refraction of greater than 1.00 DC. Two of the participants were soft contact lens wearers, but they ceased lens wear one week prior to participation in the experiment and did not wear lenses for the duration of their involvement in the experiment. To limit the potential confounding influence of ocular diurnal variations upon the results (Chakraborty et al., 2011), all three experimental conditions were tested at approximately the same time of day between 9 am and 2 pm on different days, in randomized order, for each subject.

2.1.1. Pharmacologic agents

Only the right eyes were treated with either: one drop of 2% homatropine hydrobromide, or one drop of 2.5% phenylephrine hydrochloride or placebo (consisting of 0.3% hydroxypropyl methylcellulose) over three separate days, with a different pharmacological agent tested at each visit in randomized order. Homatropine hydrobromide is a non-selective anticholinergic agent that is closely related to atropine (although it has shorter lasting mydriatic and cycloplegic effects), while phenylephrine is a selective α_1-adrenergic agonist. The drug doses were chosen based on the dosage that is commonly used in clinical practice, since these doses are known to be safe and to have a clinically significant pharmacological effect on the iris and ciliary body function. The doses are also predicted to exceed the published ED50 values of phenylephrine (Theofilopoulos et al., 1988) and homatropine (Smith, 1976). To prevent contamination of a trial due to the residual action of a previously administered agent, a washout period up to ten times the terminal elimination half-life of the drug was