Probing peripheral and central cholinergic system responses

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**Objective:** The pharmacological response to drugs that act on the cholinergic system of the iris has been used to predict deficits in central cholinergic functioning due to diseases such as Alzheimer’s disease, yet correlations between central and peripheral responses have not been properly studied. This study assessed the effect of normal aging on (1) the tropicamide-induced increase in pupil diameter, and (2) the reversal of this effect with pilocarpine. Scopolamine was used as a positive control to detect age-dependent changes in central cholinergic functioning in the elderly.

**Design:** Randomized double-blind controlled trial.

**Participants:** Ten healthy elderly (mean age 70) and 9 young (mean age 33) volunteers.

**Interventions:** Pupil diameter was monitored using a computerized infrared pupillometer over 4 hours. The study involved 4 sessions. In 1 session, tropicamide (20 µL, 0.01%) was administered to one eye and placebo to the other. In another session, tropicamide (20 µL, 0.01%) was administered to both eyes, followed 23 minutes later by the application of pilocarpine (20 µL, 0.1%) to one eye and placebo to the other. All eye drops were given in a randomized order. In 2 separate sessions, a single dose of scopolamine (0.5 mg, intravenously) or placebo was administered, and the effects on word recall were measured using the Buschke Selective Reminding Test over 2 hours.

**Outcome measures:** Pupil size at time points after administration of tropicamide and pilocarpine; scopolamine-induced impairment in word recall.

**Results:** There was no significant difference between elderly and young volunteers in pupillary response to tropicamide at any time point (p > 0.05). The elderly group had a significantly greater pilocarpine-induced net decrease in pupil size 85, 125, 165, and 215 minutes after administration, compared with the young group (p < 0.05). Compared with the young group, the elderly group had greater scopolamine-induced impairment in word recall 60, 90, and 120 minutes after administration (p < 0.05).

**Conclusion:** There is an age-related pupil-
According to the cholinergic hypothesis of memory function, certain changes in memory are associated with a decline in central cholinergic function. The central cholinergic system is known to play an important role in learning, cognition and memory. This has been suggested that changes in the central cholinergic system is known to play an important role in learning, cognition and memory. This has been observed in various studies involving both human and animal models, in which centrally acting cholinergic agonists and antagonists have been used to augment cognitive function. Recent studies have also shown that changes in the binding of specific ligands for muscarinic receptor subtypes in elderly rats. These changes have been modelled with scopolamine, a muscarinic cholinergic antagonist. A classic study conducted in 1974 demonstrated that young normal subjects treated with scopolamine exhibited significant decreases in performance of certain cognitive tests. However, this decreased level of cognition was not significantly different from elderly controls at baseline. It has also been shown that the cholinesterase inhibitor physostigmine can block most of the cognitive deficits associated with scopolamine treatment, whereas amphetamines and other stimulants do not block these deficits. This result suggests that the decline in cognitive function seen in aging, like the effects of scopolamine, may be caused by a decrease in central cholinergic system functioning.

Currently, there are no pharmacologically based, noninvasive peripheral probes to monitor or predict central cholinergic function. Such peripherally acting probes would be advantageous because, unlike centrally acting cholinergic probes, such as scopolamine, they would be noninvasive and would not cause adverse central cholinergic effects. Recently, some evidence has suggested that changes in the central cholinergic system may be accompanied by changes in peripheral cholinergic function.
ergic function. For example, adults with Down’s syndrome over the age of 30 have memory impairment, dementia and neuropathologic lesions (e.g., neurofibrillary tangles) characteristic of central cholinergic deficit. In these individuals, the cholinergic antagonist atropine caused a significantly greater increase in heart rate than in control subjects, while topically applied atropine and tropicamide (a muscarinic antagonist) eye drops caused a significantly greater increase in pupil diameter.

Alzheimer’s disease (AD) is another disorder in which there is a widespread decrease in central cholinergic function and a pattern of brain lesions similar to that in Down’s syndrome. One group has observed that patients with AD exhibit a significantly greater increase in pupil size in response to tropicamide eye drops than age-matched controls. However, many groups have attempted and failed to replicate that result. A few groups have used a slightly different approach, observing the pupillary response to pilocarpine, a muscarinic agonist. In contrast to the tropicamide literature, all of the studies of pilocarpine indicate that it may be sensitive to changes in central cholinergic function, as patients with AD showed a hypersensitive response to pilocarpine in comparison with age-matched controls.

This study was performed to develop a peripheral probe that would be able to detect age-related changes in central cholinergic function. The objective of the study was to assess the effect of normal aging on (1) tropicamide-induced increase in pupil diameter, and (2) the reversal of this effect with pilocarpine in healthy elderly and young volunteers. We used scopolamine as a positive control to detect age-dependent changes in central cholinergic system function in the elderly.

Methods

Subjects

We recruited 10 elderly (older than 55 years) and 9 young (18 to 40 years) healthy volunteers through advertisements in local newspapers. Demographic information, including education, weight, ethnic background and cognitive status, was collected before the study. Cognitive status was assessed with the Mini-Mental State Examination (MMSE) before the study, and the subjects’ scores were required to be greater than 28 to rule out significant cognitive impairment. Subjects had good to excellent health, as assessed by the General Health Questionnaire, and underwent a general ocular examination, including slit-lamp biomicroscopy, by an ophthalmologist (C.B.). An electrocardiogram was obtained from each elderly subject and was read by a cardiologist before the study. Exclusion criteria were contraindications to any of the study drugs (tropicamide, pilocarpine or scopolamine), including a shallow anterior ocular chamber, history of intraocular surgery, cloudy cornea, glaucoma, any sign of cataracts, or significant cardiac abnormality. Subjects continued to receive any concomitant medications during the study, and these medications were assessed by interviews with the subjects and their physicians when necessary. Subjects abstained from alcohol, smoking and caffeine-containing food or beverages for at least 12 hours before and during test sessions, and were advised to get a good night’s rest before each session. All subjects gave written informed consent and received compensation for their participation in the study. This study was approved by the Research Ethics Board of the Sunnybrook and Women’s College Health Sciences Centre.

Study design

For each of 4 study sessions, subjects arrived at the Psychopharmacology Research Laboratory at 10 a.m. The laboratory light conditions were standardized to an illumination of 600 lux. Sessions followed a balanced and randomized double-blind study design and were separated by a minimum of 72 hours. During one session, subjects were administered tropicamide (20 µL eye drop, 0.01%) to one eye and placebo (sodium chloride, 20 µL eye drop, 0.9%) to the other eye, in a randomized order. Pupil diameter was measured twice at baseline and at 17 time points over a period of 240 minutes by a computerized infrared pupillometer. In another session, tropicamide (20 µL, 0.01%) was administered to both eyes, followed 25 minutes later by the application of pilocarpine (20 µL, 0.1%) to one eye and placebo to the other eye, in a randomized order. Pupil diameter was measured at 13 time points over a period of 215 minutes by a computerized infrared pupillometer. In another session, tropicamide (20 µL, 0.01%) was administered to both eyes, followed 25 minutes later by the application of pilocarpine (20 µL, 0.1%) to one eye and placebo to the other eye, also in a randomized order. Pupil diameter was measured at 13 time points over a 215-minute period after pilocarpine administration. All eye drops were instilled using a precision micropipette into the lower conjunctival cul-de-sac with the subject supine. In addition, following administration of each set of eye drops, the investigator pressed his or her fingers on the subject’s nasolacrimal duct for 1 minute.
In 2 separate test sessions, an indwelling catheter was inserted into the cephalic vein of the less dominant forearm. After baseline assessments, scopolamine (0.5 mg) or placebo was administered intravenously via slow injection over 2 minutes. Cognitive function was measured at baseline and at 30, 60, 90 and 120 minutes after drug administration. At these time points, pupil diameter was also measured.

Assessment of scopolamine effect

Scopolamine-induced impairment of memory and learning was assessed by a modified Buschke Selective Reminding Test, which has been used in previous studies of scopolamine by other investigators. This test detects the cognitive impairment induced by scopolamine in both young and elderly individuals.

Buschke Selective Reminding Test. The test was performed at each of the 5 assessment time points and consisted of a 12-word list in which the words have the same frequency of use as they do in the English language and were categorically unrelated. Equivalent versions of the word lists were constructed and a different set was used at each time point after scopolamine or placebo administration. All 12 words were read to the subject (1 word every 3 seconds), and the subject was asked to recall as many words as possible during a 55-second timeframe. This was followed by a 30-second pause, after which the investigator read only the words that were not recalled by the subject during the previous recall period. The subject was again asked to recall as much of the 12-word list as possible. This procedure was repeated 7 times (for a total of 8 recall attempts). However, if the subject recalled all 12 words in 2 successive trials, the test was discontinued and maximum score (12) was assigned for each of the remaining recall trials. The total number of words recalled in the 8 trials was used as a measure of memory/learning at each time point.

Visuospatial praxis, psychomotor function, and subject-rated sedation. Visuospatial praxis was assessed with a block-construction subtest of the Wechsler Adult Intelligence Scale (WAIS). The test was administered at baseline and at 90 minutes after administration of scopolamine or placebo. The blocks used in each test were identical, with 2 red sides, 2 white sides and 2 sides that are red and white. The subject was asked to make specific designs with the blocks during a specified limited time interval.

The digit symbol substitution subtest (DSST) of the WAIS was also performed at each time point to assess psychomotor function. For the DSST, subjects were presented with a set of symbols and matching numbers and were asked to draw the correct symbol below each number during a 90-second interval.

Subject-rated sedation was assessed at each time point using a 20-cm visual analogue scale that ranged from “not at all” at the left end to “extremely” at the right.

Pupillometry

A previously validated infrared pupillometer connected to a personal computer was used to measure pupil diameter. The apparatus consisted of 4 infrared diodes that illuminated the eye, an infrared-sensitive video camera, and a small computer-controlled display television for the eye. Each captured image was processed to determine the edge of the pupil, and the maximal diameter value out of 40 computer-generated diameter measurements was recorded. During pupillometry, the subject was seated in an armchair, with the chin placed on an adjustable chin-rest connected to the camera stand while the eyes were fixated on a target at a standardized distance.

Data analysis

Data were analyzed using the Statistical Analysis System (SAS), version 6.11 (SAS Institute Inc., Cary, NC, 1996). The data on net increases in pupil size after challenge with tropicamide and placebo were expressed at each time point as \[ \frac{\text{pupil diameter after tropicamide} - \text{the corresponding pupil diameter after placebo}}{\text{pupil diameter after placebo at that time point}} \times 100 \] . For the pilocarpine data, the net decrease in pupil size was expressed as \[ \frac{\text{pupil diameter after placebo} - \text{the corresponding pupil diameter after pilocarpine}}{\text{pupil diameter after placebo at that time point}} \times 100 \]. The pupil diameter of the treated eye was compared with the placebo-matched pupil diameter at each given time point to account for the potential contribution of tonic sympathetic activity to pupil diameter, which would affect both eyes equally, over the course of the study session. The tropicamide and pilocarpine data were tested for significant differences by 2-way repeated measures analysis of variance (ANOVA), with 2-way interaction. The 2 variables in the ANOVA were age and time, where time was the...
repeated-measures variable. The scopolamine data were analyzed using a 3-way repeated measures ANOVA, with 3-way interaction. The variables in this ANOVA were age, treatment and time, with time as the repeated-measures variable. When ANOVA was significant ($p < 0.05$), further multiple comparisons were performed at each time point using Student’s $t$-test with Bonferroni correction, which maintained the significance level at $p < 0.05$.

**Results**

**Subjects**

Ten elderly (mean age 70, standard error of the mean [SEM] 2 years, range 59 to 79; years of education 14 SEM 1; weight 75 SEM 5 kg) and 9 young (mean age 33 SEM 2, range 18 to 40; years of education 17 SEM 1; weight 73 SEM 5 kg) healthy volunteers were recruited. There was no significant difference between elderly and young subjects in education and weight, or in cognitive status (elderly mean MMSE score 29 SEM 0.2; young 30 SEM 0.3, $p > 0.05$). All subjects were of European descent except for 1 elderly subject (Caribbean descent) and 2 young subjects (Korean and Afghani descent). All subjects had good to excellent health as assessed by the General Health Questionnaire. Other characteristics are given in Table 1. None of the elderly subjects screened were found to be ineligible for the study because of ocular conditions.

**Tropicamide effect on pupil size**

The time course of changes in pupil size after tropicamide administration in the elderly and young subjects is shown in Fig. 1. The ANOVA found a significant time effect ($F = 39, p < 0.05$) on pupil size, but there was no significant effect of age, or age and time ($F = 1.34, p > 0.05$) on pupillary response to tropicamide. The mean peak increase in pupil diameter was observed 50 minutes after tropicamide administration and was not significantly different between the 2 age groups ($p > 0.05$).

**Pilocarpine effect on pupil size**

The time course of the pilocarpine effect on pupil size, following the tropicamide-induced increase in pupil size, is presented in Fig. 2. The pilocarpine-induced net

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decrease in pupil size was faster and larger in the elderly group than in the young group \( (p = 0.003) \). The ANOVA found a significant effect of time \( (F = 19.01, p < 0.05) \) as well as age and time \( (F = 2.51, p < 0.05) \) on pupil response to pilocarpine. The peak pilocarpine effect on pupil size was observed at the 85-minute time point. The elderly subjects had a significantly greater \( (p < 0.05) \) mean net decrease in pupil size at the 85-, 125-, 165- and 215-minute time points (34% SEM 2.1%, 30.6% SEM 3.0%, 28.9% SEM 2.9%, 23.9% SEM 2.4%, respectively, compared with placebo) compared with the young subjects (20.3% SEM 5.2%, 15.8% SEM 5.4%, 14.9% SEM 3.0%, 8.8% SEM 4.9%, respectively, compared with placebo). There was no significant difference in pupil size between the 2 groups at baseline (5.2 mm for the young group and 4.8 mm for the elderly group, \( p > 0.05 \)). The mean absolute decrease in pupil size for the elderly group at the 85-, 125-, 165-, and 215-minute time points was 1.5, 1.3, 1.1 and 0.8 mm, respectively, compared with 0.7, 0.4, 0.3 and 0.1 mm, respectively, for the young subjects. Sex, iris colour and ethnic background did not affect pilocarpine effect on pupil size \( (p > 0.05) \).

**Scopolamine effect on cognitive function**

The time course of scopolamine-induced impairment in word recall for the Buschke Selective Reminding Test is shown in Fig. 3. The ANOVA found a significant effect of time \( (F = 7.18, p < 0.05) \) as well as age, and time and treatment \( (F = 3.06, p < 0.05) \) on word recall after scopolamine administration. The impairment in word recall was greater in the elderly subjects than in the young subjects 60 (elderly 41.7% SEM 10.8% of baseline; young 58.7% SEM 9.0%), 90 (elderly 43.1% SEM 12.5%; young 60.6% SEM 7.8%), and 120 (elderly 47.1% SEM 12.7%; young 103.0% SEM 7.6%) minutes after scopolamine administration \( (p < 0.05) \). There were no significant differences in visuospatial praxis, DSST scores, subject-rated sedation, and scopolamine effect on pupil size between the elderly and the young subjects \( (p > 0.05) \).

![Fig. 1: Time course of tropicamide effect on pupil diameter in elderly and young subjects (means and standard error bars).](image)
Sex and ethnic background did not significantly influence the scopolamine effects ($p > 0.05$).

**Relation between peripheral and central cholinergic probes**

The effect of scopolamine-induced impairment on word recall 90 minutes after administration for each individual subject is illustrated in Fig. 4A. The effect of pilocarpine-induced net decrease in pupil diameter at the 125-minute time point for each individual subject is presented in Fig. 4B. All subjects demonstrated both concomitant memory impairment due to scopolamine and decreased pupil diameter due to pilocarpine administration, except subjects 1 and 11. However, there was no significant linear correlation between the 2 responses ($r = 0.13$, $p = 0.60$).

**Discussion**

This study is the first to compare the time course of pupil response to tropicamide in normal elderly and young subjects. The effect of a standard dose of tropicamide (20 µL, 0.01%) on pupil diameter was measured using a computerized infrared pupillometer over a long timeframe (240 minutes) in order to assess the tropicamide effect carefully. Only a few of the previous studies examining tropicamide have examined the time course of the pupil-dilating effect beyond 60 minutes, as the peak effect is reached 30 to 45 minutes after application of the drug.

Our results indicate that tropicamide does not elicit possible functional changes in the cholinergic system in the iris due to normal aging in 2 groups with known differences in central cholinergic function. This is in agreement with the other studies that did not detect differences in central cholinergic function between patients with AD and normal age-matched controls. A previous study suggested that an increased pupil response to dilute tropicamide might be a diagnostic market for AD. That study found a mean 23% increase...
in pupil diameter from baseline in patients with AD compared with a 5% increase in healthy age-matched controls. However, studies attempting to replicate those results were unable to distinguish between the 2 groups, as the responses of both the control groups and patients with AD in later studies were similar to the responses in patients with AD in the original study.19 As a whole, these results indicate that it is still uncertain whether pupillary response to tropicamide can distinguish between the different levels of central cholinergic system activity in healthy elderly and young subjects, and in healthy elderly subjects and patients with AD.

Pilocarpine induced a net decrease in pupil diameter that was faster and greater in the elderly group than in the young group. This result indicates that pilocarpine may be a peripheral marker for the age-related decline in central cholinergic function. This supports a limited number of studies that may have also detected cholinergic differences between patients with AD and age-matched controls, as those studies observed a significantly larger miotic response to pilocarpine in the patients with AD.20–22 However, there were limitations in the methodology of these studies. These include a lack of placebo controls, a lack of a computerized pupillometer, and the assessment of pupil diameter at a single time point. This study improves on the previous studies by using a randomized placebo-controlled design and a computerized pupillometer to record more frequent measurements over a longer timeframe.

The tropicamide–pilocarpine challenge test was designed to capitalize on the homeostatic cholinergic control of pupil size in such a way that changes in diameter would be maximized. It was expected that initial dilation of the pupil with tropicamide would allow for

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**Fig. 3:** Time course of changes in word recall after scopolamine administration in elderly and young subjects, compared with placebo (means and standard error bars). *significant difference between the elderly and the young subjects.
greater miotic changes due to administration of pilocarpine. While this study found that the magnitude of the change was increased, the length of time required for contraction of the pupil was lengthened by the initial dilation with tropicamide. Our group has also examined the possibility that pilocarpine administration alone may be a peripheral marker for changes in central cholinergic function. To determine the usefulness of this procedure, we performed a challenge test with pilocarpine alone on 4 of the healthy elderly subjects and compared individual results from both methods (data not published). The pilocarpine challenge test employs the same techniques as the tropicamide–pilocarpine challenge test except that the pupils are not previously dilated with tropicamide. The maximum percentage decrease of pupil size from baseline was mean 29.6% SEM 4.03% for pilocarpine challenge alone (at 45 minutes after administration) compared with a mean 29.7% SEM 3.06% for tropicamide–pilocarpine challenge (at 85 minutes after administration). When comparing individual responses, the net difference between the 2 procedures was mean 0.95% SEM 0.50%. A paired t-test showed that there was no significant difference in the pupil response to pilocarpine versus tropicamide followed by pilocarpine for elderly adults ($p > 0.05$). Furthermore, using only pilocarpine is advantageous because it requires much less time than tropicamide and pilocarpine, and is a much simpler test.

![Graph](image.png)

Fig. 4: Individual changes in word recall after scopolamine administration (A) and pilocarpine effect on pupil diameter (B) in the elderly (1-10) and the young (11-19) subjects. Subjects are arranged in decreasing order of impairment on word recall induced by scopolamine in A. The same arrangement of subjects is used in B.
of central cholinergic function. This has led our group to use pilocarpine alone in our current studies involving elderly subjects and patients with AD.

As a whole, these results raise the question of why individuals with decreased central cholinergic functioning appear to show a hypersensitive response to pilocarpine and not to tropicamide. Some possible explanations include (1) differences in absorption due to differences in the molecular size and charge of the 2 drugs, (2) differences in mechanisms of action between agonists and antagonists, and (3) differences in receptor specificity of pilocarpine and tropicamide for various muscarinic receptor subtypes and changes in various subtype populations in aging. Alternative explanations include altered corneal permeability, dryness of eyes, tear production, blink rate, colour of the iris, and genetic factors, all of which could affect the absorption of eye drops and thus the concentration of the 2 drugs at the receptor level.

The elderly have been shown to be more sensitive to the cognitive effects of scopolamine than young individuals. It has been suggested that this may be due to central cholinergic system deficit associated with aging. This study assessed the effects of scopolamine on memory in the elderly and the young groups and confirmed that the elderly group did indeed have an increased sensitivity to scopolamine, as demonstrated by a greater improvement in word recall.

No significant linear correlation was found between individual responses to scopolamine and the corresponding decrease in pupil diameter in response to pilocarpine. There are several possible explanations as to why we were unable to detect such a relation in this study. First, it may be explained by differences in receptor pharmacology. The density and distribution of muscarinic receptor subtypes within different brain regions are varied compared with each other and with the iris. In addition, changes in muscarinic receptor subtypes peripherally in the iris may not mirror those occurring centrally. There have not been any studies characterizing changes in muscarinic receptors in the brain in aging, although several such studies have been conducted in patients with AD. As well, no published studies have examined the changes in muscarinic receptor subtypes in the iris in aging or AD. Similarly, scopolamine and pilocarpine do not have the same muscarinic receptor subtype specificity. Interestingly, though, literature exists to support both as M₂-selective agents, although other studies list them as non-selective drugs. In light of this controversy, it is conceivable that the use of another eye drop, with an established selectivity, would result in a linear correlation between central and peripheral probes. Second, the instrument used to measure cognitive impairment, the Buschke Selective Reminding Test, may not have been the ideal tool for this purpose. The literature indicates variation in the length of the word lists and the words themselves used for different experimental designs. The word lists constructed for this study may not have been sensitive to the magnitude of central cognitive deficit. Furthermore, the responses to the test may not be correlated to the peripheral probe, and another cognitive test may have been a more appropriate choice. A third possibility is simply that there is no relation between the central and peripheral cholinergic systems. However, in light of this study and others, it remains likely that a relation between peripheral and central responses does exist, but was not detected by the design of this study. For example, in the elderly group, 3 subjects had idiosyncratic responses: one had an early and accelerated response to pilocarpine; the second had an exaggerated response to scopolamine (floor effect); and the third had no response to scopolamine. Thus, the responses of 2 patients may be an artifact generated by using scopolamine as a model, and the third is unexplained. When these subjects were removed from the analysis, we found a significant correlation between the responses ($r = 0.66, p < 0.05$).

Further evidence to support the link between central and peripheral cholinergic systems is the identification of AD pathology in the Edinger-Westphal nucleus (EW) of patients with AD. The EW nucleus is known to have a role in controlling pupillary constriction and may mediate between the sympathetic and parasympathetic innervation of the iris musculature. The discovery of a peripheral marker for the central cholinergic system has many possible implications in the area of cognitive decline related to decreased central cholinergic function. However, the potential for a pilocarpine eye drop test as a diagnostic tool for AD has yet to be determined. We see our peripheral probe as an index of central cholinergic function and not as a potential diagnostic tool for AD. One may argue that this distinction is merely one of semantics; however, the pathology of AD is not limited to cholinergic deficits, as evidence also shows disruptions in neurochemical markers in the noradrenergic, serotonergic, dopaminergic and histaminergic systems. Because of the heterogeneity of
this disease, a probe of the central cholinergic system may lack the specificity needed to be useful as a diagnostic test for AD.

We believe that this procedure could be better used to monitor central cholinergic decline in the subset of AD patients with severe cholinergic pathology. It may also prove useful in predicting treatment response to cholinergic therapies for AD. This includes treatments such as the cholinesterase inhibitors, which increase the activity of the endogenous central cholinergic system. As well, it has been suggested that a minimal level of central cholinergic function must be present for effective treatment. Our probe may determine when there is enough cholinergic damage that it is appropriate to discontinue treatment.

From our results, we conclude that administration of dilute tropicamide eye drops is unable to detect potential age-related changes in the peripheral cholinergic system of the iris. This is the first study to indicate that pilocarpine may detect changes in the peripheral cholinergic system due to normal aging. The result with pilocarpine may lead the way for the potential usefulness of this drug for tests in AD and other disorders of the central cholinergic system.

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References


