Age and Ageing 1996;25:432–438

Changes in Autonomic Function with Age: A Study of Pupillary Kinetics in Healthy Young and Old People

P. BITSIOS, R. PRETTYMAN, E. SZABADI

Summary

The object of the study was to compare resting pupil diameter in darkness and light, and the pupillary darkness and light reflexes between a group of young and elderly healthy subjects.

Twelve young (eight men, four women; median age 19.5 years) and 14 elderly subjects (six men, eight women; median age 69 years) participated.

Pupil diameter was monitored with an infra-red television pupillometer. Resting pupil size was measured in light (16 and 32 Cd m^{-2}) and in darkness. The darkness reflex was elicited by switching off the ambient illumination (16 Cd m^{-2}) for 1 s. The light reflex was elicited in darkness by short (200 ms) pulses of green (peak wavelength 565 nm) light at four ascending stimulus intensities (8.5×10^{-3}, 7.0×10^{-2}, 0.43 and 1.84 mW cm^{-2}). The amplitude (mm) and maximum velocity (mm s^{-1}) of the darkness reflex and the latency (ms), amplitude (mm), maximum constriction velocity (mm s^{-1}) and 75% recovery time (s) of the light reflex were measured.

The resting pupil diameter was found to be smaller in the elderly group at all three illumination levels ($p = 0.001$). The amplitude and maximum dilatation velocity of the darkness reflex were smaller for the elderly group ($p = 0.001$). The amplitude of the light reflex at the three highest light intensities and maximum constriction velocity at all light intensities were smaller in the elderly group ($p = 0.002$). Seventy-five per cent recovery time was longer in the elderly group ($p = 0.02$). There was no difference in the latency of the light reflex response between the two groups.

The reduced pupil size, diminished darkness reflex amplitude and velocity, and prolonged recovery time of light reflex are consistent with sympathetic deficit in old age. Although the reductions in light reflex amplitude and constriction velocity in the elderly group at first sight would indicate a parasympathetic deficit in old age, they are more likely to be secondary to the grossly diminished pupil size.

Keywords: Pupil, Darkness reflex, Light reflex, Ageing.

Introduction

Among the recognized clinical characteristics of normal ageing are alterations in function of the autonomic nervous system. Much of the evidence concerning changes in autonomic physiology with age derives from studies of the cardiovascular system. These suggest diminished β-adrenoceptor-mediated functions [1, 2], vasoconstriction responses, baroreflexes [3] and heart rate variability [4]. However, interpretation of these findings is complicated by the possible confounding effect of haemodynamic factors (e.g. ischaemic heart disease) not secondary to changes in autonomic nervous system activity [4]. Other studies have suggested that a change in sweat gland responsiveness in older people may reflect a peripheral sympathetic deficit [5, 6].

In order to investigate the nature of the age-related changes in autonomic function further, we studied the static and dynamic characteristics of the pupil by means of infra-red television pupillometry in healthy young and old subjects. The pupil has an exclusively autonomic innervation, pupil diameter reflecting the balance between sympathetic and parasympathetic tone, thus constituting a sensitive test system of central and peripheral autonomic activity. Particular components of the light (see Figure 1: top) and darkness reflexes (see Figure 1: bottom) such as amplitude, constriction/dilatation velocities and recovery time are known to reflect activity in the sympathetic and parasympathetic systems differentially [7].

In the present study we investigated the relationship between the recognized decline in resting pupil diameter with age [7–11] and changes in pupillary

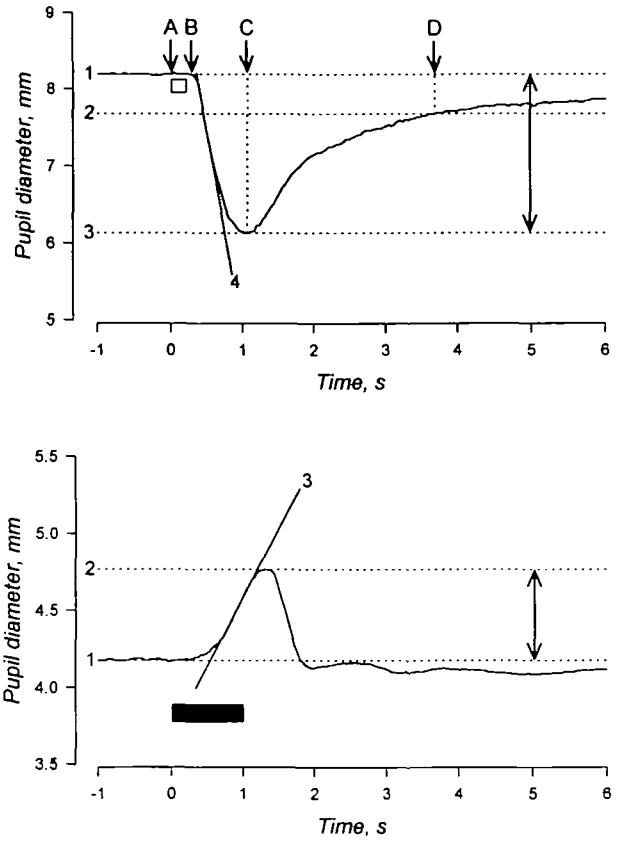

Figure 1. Examples of light (top) and darkness (bottom) reflex responses. *Light reflex (top):* horizontal bar: light stimulus; 1: initial pupil diameter; 2: 75% recovery; 3: pupil diameter at maximal constriction; 4: line representing slope of steepest segment of constriction curve; A: onset of light stimulus; B: onset of response; C: time of maximal constriction; D: time at which 75% recovery is attained; 1 – 3 amplitude; A–B: latency; C–D: 75% recovery time. *Darkness reflex (bottom):* horizontal bar: darkness stimulus; 1: initial diameter; 2: pupil diameter at maximal dilatation; 3: line representing slope of steepest segment of dilatation curve; 2 – 1: amplitude of dilatation.

kinetic parameters of the light and darkness reflexes, only some of which have been previously studied in old age [8, 10–12].

Methods

Subjects: Healthy young subjects and elderly subjects were recruited to the study. Young subjects were recruited by advertisement; they were students and hospital workers. Elderly subjects were recruited via personal contact with the Hospital Volunteer Service at Queen's Medical Centre, Nottingham, and the local branch of the Alzheimer's Disease Society (spouses of patients). Subjects with any history or presence of disorders of central or autonomic nervous systems, psychiatric illness, ocular pathology, hearing problems or taking any medication were excluded. Initially, 12 healthy young subjects and 20 healthy elderly subjects were recruited. No subjects refused to participate; however, six elderly subjects (>60 years) were excluded on the basis of the exclusion criteria. The median age of the young subjects (eight men, four women) was 19.5 years (range 19–26) and the median age of the old subjects (six men, eight women) was 69 years (range 61–79). The sample sizes were chosen on the basis of power estimations based on published data on the variance of resting pupil size in healthy subjects [7] and the known rate of decline in resting pupil size with age [10].

Details of experimental session: An infra-red binocular television pupillometer (Applied Science Laboratories, Waltham, MA) was used for the recording of subjects' resting pupil diameter in light, in the dark, and of light and darkness reflexes.

The experimental session started with a 45-s recording of resting pupil diameter in two conditions of ambient light (32 and 16 $Cd\,m^{-2}$). The mean diameter from each recording was taken as the mean resting pupil diameter for each subject for the two illumination conditions. After 5 min of light adaptation in the 16 $Cd\,m^{-2}$ condition, the average of 12 darkness reflexes elicited by 1-s dark periods at 25-s intervals was taken for each subject. After the recording of the darkness reflex, the lights were switched off and the pupil diameter was recorded at intervals during dark-adaptation.

After 10 min of dark-adaptation a series of 12 light reflexes was elicited by short (200 ms) light stimuli generated by a green (peak wavelength 565 nm) light emitting diode positioned 1 cm in front of the subject's right cornea. The stimuli consisted of three pulses at each of four ascending stimulus intensities (8.5×10^{-3}, 7.0×10^{-2}, 0.43 and 1.84 $mW\,cm^{-2}$ respectively). For each stimulus intensity the three light reflexes were averaged. The inter-stimulus interval was 25 s. At the end of the session, another 45-s recording of the resting pupil diameter was taken before the lights were switched on. Pupillary measures were recorded digitally and stored on a floppy-disk for off-line analysis.

For the light reflex, the parameters measured were the latency (time elapsed between the onset of stimulus and onset of response), amplitude (distance between pre-stimulus resting pupil size and the deepest trough of the response), 75% recovery time (time taken from the peak of the response to obtain 75% recovery), and the maximum constriction velocity (V_{cm}) (see Figure 1: top). For the darkness reflex, amplitude of dilatation and maximum dilatation velocity (V_{dm}) were measured (see Figure 1: bottom). Maximum constriction velocity ($mm\,s^{-1}$) was obtained by dividing the reduction in pupil diameter by the time over which it occurred at the steepest segment of the response curve; maximum dilatation velocity ($mm\,s^{-1}$) was obtained similarly at the steepest segment of the dilatation curve.

Data analysis: Descriptive statistics (means and standard errors) were calculated for each pupillary variable within each of the two groups (young and old). The distribution of each variable was assessed by calculating the skew and kurtosis indices. As in no case did either index deviate significantly from zero, parametric statistics were used. Data were investigated by means of unpaired t tests to examine differences between the young and old groups for each parameter. As the parameters of the light reflex may reflect both the intensity of the light stimulus and the age of the subject, two-factor analyses of variance (ANOVA) were also performed (age group × light intensity as a within-subject factor). Furthermore, as each of the kinetic measures may depend on resting pupil size and may be related to other kinetic parameters, the interdependence between these measures was investigated by means of Pearson's correlation coefficients and analysis of covariance between the young and old groups.

Results

Resting pupil diameter: Mean resting pupil diameters for the two groups, in both conditions of ambient light (32 and 16 Cd m^{-2}), and in all consecutive recordings in the dark, are shown in Figure 2. Unpaired t tests showed that the resting pupil diameter was significantly smaller in the elderly group in all conditions ($p = 0.001$).

Darkness reflex: Both parameters measured (amplitude and maximum dilatation velocity) were significantly lower in the group of older subjects (see Figure 3; unpaired t tests: $t = 5.00$; $df = 24$; $p = 0.001$ and $t = 5.17$; $df = 24$; $p = 0.001$ respectively). Maximum dilatation velocity of the darkness reflex was significantly correlated with initial diameter ($r = 0.47$, $p = 0.01$). Analysis of covariance with initial diameter as a covariate showed that, whilst there was a significant effect of initial diameter on V_{dm} ($F = 7.25$, $df = 1, 23$; $p = 0.013$), the residual effect of group (age) remained significant ($F = 23.01$, $df = 1, 23$; $p = 0.001$).

Light reflex: The mean amplitude, maximum constriction velocity (V_{cm}), latency, and the 75% recovery time for the four graded light intensities in both groups are shown in Figure 4. Figure 5 shows the extent to which amplitude and V_{cm} were correlated with initial diameter. Univariate ANOVAs for each separate light intensity showed significantly smaller amplitudes and maximal constriction velocities in the elderly group for all stimulus intensities except for the lowest one used. However, when initial diameter was taken as a covariate, the residual group-wise differences were no longer significant. One young subject's recovery time data were excluded from the analysis because they were abnormally prolonged consistent with the 'dazzling syndrome'. This is a benign condition characterized by very long recovery times at low light intensities such as would normally only be observed with very intense dazzling light [9].

Two-factor ANOVAs with repeated measures, with light intensity as the within subject factor, showed significant main effects of light intensity ($F = 133.2$; $df = 3, 73$; $p = 0.001$) and group ($F = 11.6$; $df = 1, 24$;

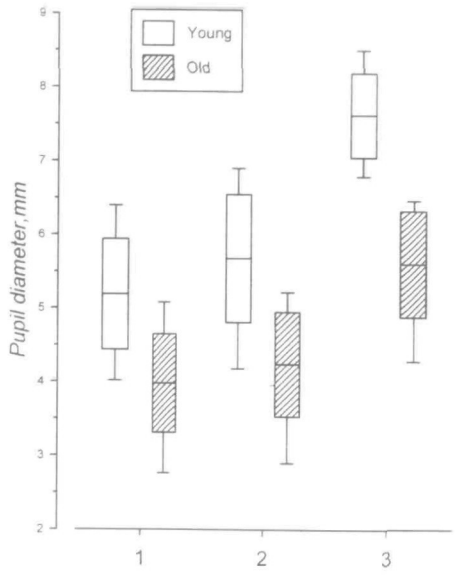

Figure 2. Resting pupil diameter under three illumination conditions. 1: 32 Cd m^{-2}; 2: 16 Cd m^{-2}; 3: darkness (90 s after lights off). The horizontal lines are group means, the 'boxes' are SD, the 'whiskers' are extreme values in each group. In the dark, pupil diameter remained constant after 90 s: there was no significant difference between readings at 90 s and 40 min.

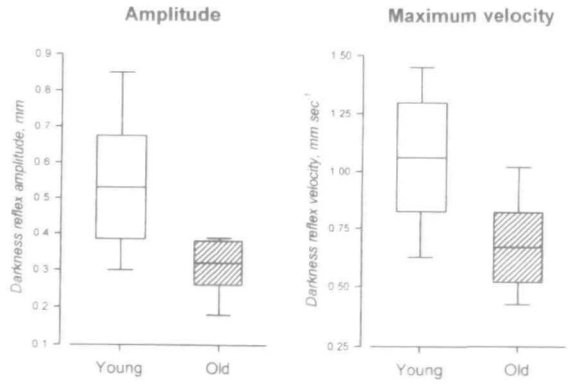

Figure 3. Comparison of the parameters of the darkness reflex between young (□) and old (■) subjects. For conventions see Figure 2.

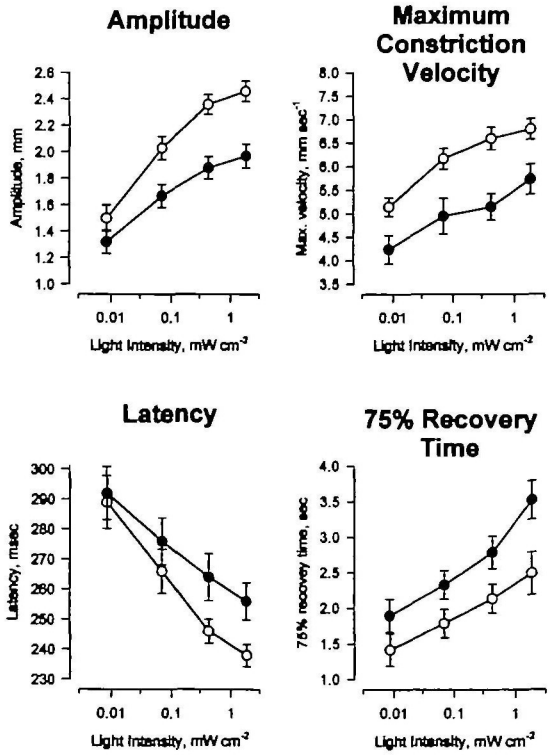

Figure 4. Comparison of the parameters of the light reflex between young (○) and old (●) subjects. Vertical bars are SE mean.

	Amp.a	Amp.b	Amp.c	Amp.d	$Diam_{dark}$
Amp. a					0.350
Amp. b					0.649**
Amp. c					0.748**
Amp. d					0.797**
V_{cm} a	0.596**				0.391
V_{cm} b		0.628**			0.458*
V_{cm} c			0.797**		0.643**
V_{cm} d				0.436	0.431
75% RTa	0.175				0.078
75% RTb		0.105			0.044
75% RTc			0.047		-0.030
75% RTd				0.034	-0.119
Latency a	-0.533*				0.054
Latency b		-0.252			-0.039
Latency c			-0.212		-0.227
Latency d				-0.407	-0.427

Figure 5. Correlation matrix for light and darkness reflex parameters. Amp: light reflex amplitude; V_{cm}: light reflex constriction velocity; 75% RT: 75% recovery time; Latency: light reflex latency. Numbers refer to each parameter for each of four stimulus intensities a–d (8.5×10^{-3}, 7.0×10^{-2}, 0.43 and 1.84 mW cm^{-2} respectively). *$p < 0.01$; **$p < 0.001$.

$p = 0.002$), and a significant interaction ($F = 4.84$; $df = 3, 72$; $p = 0.004$) for amplitude. Between-group comparisons at individual light intensity levels (Bonferoni's test) indicated that the two groups differed significantly ($p < 0.05$) at the three highest light intensities (i.e. at 7.0×10^{-2}, 0.43 and 1.84 mW cm^{-2}). Similar effects were seen for V_{cm} ($F = 25.2$; $df = 3, 72$; $p = 0.001$ and $F = 12.1$; $df = 1, 24$; $p = 0.002$ respectively; no significant interaction) and 75% recovery time ($F = 23.6$; $df = 3, 69$; $p = 0.001$ and $F = 6.2$; $df = 1, 23$; $p = 0.02$ respectively; no significant interaction) of the light reflex. For latency, there was no significant effect of group ($F = 2.26$; $df = 1, 24$; $p = 0.145$) or interaction ($F < 1$), although the effect of light intensity was significant ($F = 27.3$; $df = 3, 72$; $p = 0.001$). Analysis of covariance (ANCOVA) for amplitude with the initial diameter of the pupil as the covariate, revealed a significant effect of the regression in the case of the between- as well as the within-subject factors ($F = 4.3$; $df = 1, 23$; $p = 0.05$, and $F = 10.6$; $df = 1, 71$; $p = 0.002$ respectively). After the removal of the effect of the covariate, the residual group effect was no longer significant ($F < 1$), however, the main effects of light intensity and the interaction remained significant ($F = 150.6$; $df = 3, 71$; $p = 0.001$, and $F = 5.35$; $df = 3, 71$; $p = 0.002$ respectively). Analysis of covariance for V_{cm} with the initial diameter of the light reflex as the covariate, revealed no significant effect of the regression ($F < 1$). Analysis of covariance was not conducted in the case of latency and 75% recovery time, since no significant correlations were found between initial diameter and these measures (see Figure 5).

Discussion

Our results show, in agreement with previous reports [7–11], that elderly subjects have smaller resting pupil diameters in the dark than younger people. Furthermore, we have shown that this difference in resting pupil size between the two groups is observable at two different intensities of ambient illumination. As resting pupil diameter reflects the balance between the opposing parasympathetic (cholinergic) constrictor and sympathetic (adrenergic) dilator influences, the reduction in pupil diameter in old age may be due either to an increase in the parasympathetic influence or a reduction in the sympathetic input. Measuring the kinetic parameters of the darkness and light reflexes may enable us to dissect the two neural influences on resting pupil size.

The darkness reflex involves an increase in pupil size in response to a reduction in the intensity of ambient illumination. Electrophysiological studies indicate that a phasic darkness period has an excitatory effect on previously inhibited sympathetic activity by steady ambient illumination [13]. Thus, this response is largely mediated by sympathetic activity [10, 13], although it also depends on active inhibition of the pupilloconstrictor (Edinger–Westphal) nucleus and a consecutive reduction of the parasympathetic input to the iris [10, 14, 15]. We have found a consistent reduction in the amplitude of the darkness reflex,

together with a reduction in the maximal dilatation velocity, in the elderly group. This observation is consistent with the notion of a decreased sympathetic activity in old people, although a contribution from an increase in parasympathetic drive cannot be excluded. However, the latter influence is more prominent at high levels of ambient illumination [10] and, since we recorded the darkness reflex in fairly dim ambient illumination ($16\,Cd\,m^{-2}$), it is likely that the reduced amplitude and velocity of the darkness reflex reflect mainly a sympathetic deficit.

The different kinetic components of the light reflex reflect the successive activation of the parasympathetic and sympathetic inputs to the iris. There is evidence that the latency and the amplitude of the light reflex are due almost exclusively to parasympathetic activation, and it has been suggested that the recovery time is largely influenced by sympathetic activation [7]. Thus, drugs with an affinity for muscarinic cholinoceptors prolong the latency and reduce the amplitude [16], whereas drugs reducing the sympathetic input prolong the recovery time [17]. In the present study we have found that the old subjects, with the exception of the lowest light intensity, have reduced light reflex amplitudes, with a reduction in maximal constriction velocity but without any significant change in light reflex latency, and a prolongation of recovery time.

The reduction in light reflex amplitude might indicate the operation of a reduced parasympathetic input to the iris. However, such an explanation is not likely since a reduction in parasympathetic activity would result in an increase rather than a decrease in resting pupil size. There are other factors which may have contributed to the apparent reduction in light reflex amplitude. Firstly, it is possible that the reduction in light reflex response amplitude is secondary to a reduction in resting pupil size. As resting pupil size is reduced the amplitude of the light reflex response diminishes, indicating the operation of a 'floor effect'. The operation of this floor effect becomes observable when the pupil constricts to a diameter <4 mm [18], and indeed the minimal pupil diameter after the application of the light stimulus was below this value for all stimulus intensities, except the lowest one, in the group of old subjects. This explanation seems to be contradicted by our finding of a significant interaction between age group and light reflex amplitude in the analysis of variance which remained significant even after the removal of the effect of initial pupil diameter by analysis of covariance. However, this is only an apparent contradiction since the effect of baseline (i.e. initial pupil diameter) on response size increases non-linearly as a function of dose (i.e. light intensity) [19, 20]. Thus the effect of baseline on response amplitude at any given light intensity level would be greater when the baseline is closer to the 'floor' (i.e. in the elderly subjects, in the present experiment).

Another possibility for an apparent reduction in light reflex amplitude is that it reflects a change in the afferent branch of the reflex (e.g. atrophy of the retinal ganglion cells resulting from retinal degeneration). Although pathological studies have demonstrated changes of this sort in old people [21], such an explanation alone is not sufficient since in our group there was no significant change in the latency of the light reflex response which is an index of afferent pupillary changes [22]. Furthermore, it is of interest that the lowest light intensity ($8.5 \times 10^{-3}\,mW\,cm^{-2}$) used evoked light reflex responses of similar amplitude in the two groups, consistent with the operation of a floor effect at the higher intensities, and we would expect that an afferent defect would be detectable even at the lowest light stimulus intensities.

We have also found a significant prolongation of the recovery time of the pupillary light reflex response in the group of old subjects. As this measure is an index of sympathetic activity [7, 17], our observation would be consistent with the operation of a reduced sympathetic input to the iris in old people. When there is a change in recovery time, it is important to consider whether this is a 'real' change or an apparent one secondary to the alteration in other kinetic parameters. It is well documented that the recovery time is closely linked to light reflex amplitude, more intense light stimuli evoking responses with larger amplitudes which take longer to recover [7]. Therefore, it is noteworthy that in the present study the reduction in light reflex amplitude was accompanied by *an increase*, rather than a decrease, in recovery time, indicating that the observed change is likely to reflect a genuine decrease in sympathetic input. The anatomical location of the sympathetic deficit remains to be established. It is unlikely that the sympathetic deficit in old age is due to a peripheral post-ganglionic lesion. Such a lesion would predict an absent mydriatic response to locally instilled indirectly acting sympathomimetic amines (e.g. hydroxyamphetamine) because of degeneration of the sympathetic terminals in the iris dilator muscle, whereas in fact the response to such agents has been shown to be normal [23, 24] in elderly subjects. Furthermore, the mydriatic response to the directly acting adrenoceptor agonist phenylephrine in elderly subjects has been shown to be enhanced [23, 24], suggesting denervation supersensitivity of the adrenoceptors in the iris. Denervation supersensitivity with intact nerve terminals at the iris dilator muscle, as evidenced by preserved responsiveness to indirectly acting sympathomimetics (see above), would be consistent with preganglionic or central deficit. Indeed, the above pattern of response to directly and indirectly acting sympathomimetic amines is also seen in younger patients with Horner's syndrome, due to preganglionic or central sympathetic lesions [25–27].

It has been suggested that the decline in resting pupil size with age was due to senile iris degeneration leading to increased rigidity [28]: such a mechanism could perhaps account for a reduced light reflex amplitude or constrictive velocity either directly or via a reduction in resting pupil size because of the floor effect mentioned earlier. A problem with this argument is that the age-related decline in pupil size progresses linearly at an

estimated rate of 0.4 mm/decade from the age of 20 years onwards [8, 10, 11] at which age age-related iris degeneration would be unlikely. A further weakness of this explanation is the observed fact that the pupils of elderly subjects dilate promptly and fully following the instillation of mydriatic eye drops [23, 24] indicating an unimpaired range and velocity of pupillary dilatation.

In conclusion, the reduction in darkness reflex amplitude and the prolongation of the recovery time of the light reflex are consistent with the notion of a decrease in sympathetic activity with old age. Such a mechanism may also explain the decline in resting pupil size with age. A simultaneous participation of a loss of supranuclear inhibition of the pupilloconstrictor nucleus [8, 10] has not been excluded with this study, and its contribution to the age-dependent decline in pupil size remains to be established. There is independent evidence that the sympathetic and parasympathetic components of the autonomic nervous system change differentially with age. Thus, Pagani *et al.* [29] reported that during tilt, ageing is progressively associated with an attenuation of the low frequency ('sympathetic') component of the heart rate power spectrum, whereas the parasympathetic response to tilt, detectable in the high frequency band, is relatively well preserved.

The observed changes in static and dynamic characteristics of the pupil in older subjects are probably mediated by alterations in autonomic function which may form part of a more general change in autonomic activity in old age. The precision and linearity of the decline of pupil size with age [7–11] suggest that the pupillary system is very sensitive and reflects most reliably the normal ageing process. The onset of the decline as early as the age of 20, far before the emergence of clinical signs of ageing, is in agreement with several lines of evidence which suggest that ageing is actually part of a larger developmental sequence and age-related changes are the result of a normal expression of a genetic programme that begins at conception and ends in death even in the absence of obvious disease [30, 31].

Acknowledgements

P. Bitsios was supported by a scholarship from the State Scholarship Foundation of Greece (IKY). We thank Professor C. M. Bradshaw for his helpful suggestions and statistical advice, and Dr G. Brimlow from the Department of Medical Physics for his help with the measurements of ambient illumination.

Key Messages

- Elderly subjects have reduced pupil diameters, consistent with a sympathetic deficit and/or parasympathetic disinhibition.
- Elderly subjects have reduced darkness reflex amplitude and dilatation velocities, consistent with a sympathetic deficit.
- Elderly subjects have prolonged recovery times of the pupillary light reflex, consistent with a sympathetic deficit.
- Caution is needed when interpreting changes in light reflex amplitude in subjects with small pupil diameters.

References

1. Kelly J, O'Malley K. Adrenoceptor function and ageing. *Clin Sci* 1984;**66**:509–15.
2. Pan HYM, Hoffman BB, Pershe RA, Blaschke TF. Decline in beta adrenergic receptor-mediated vascular relaxation with aging in man. *J Pharmacol Exp Ther* 1986;**239**:802–7.
3. Low PA. Autonomic neuropathy. *Semin Neurol* 1987;**7**:49–57.
4. Korkushko OV, Shatilo VB, Plashinda YI, Shatilo TV. Autonomic control of cardiac chronotropic function in man as a function of age: assessment by power spectral analysis of heart rate variability. *J Auton Nerv Syst* 1991;**32**:191–8.
5. Lamb K, Bradshaw CM, Szabadi E. The responsiveness of human eccrine sweat glands to choline and carbachol: application to the study of peripheral cholinergic functioning in Alzheimer-type dementia. *Eur J Clin Pharmacol* 1983;**24**:55–62.
6. Silver A, Mantagna W, Karakan I. Age and sex differences in spontaneous, adrenergic and cholinergic human sweating. *J Invest Dermatol* 1964;**43**:255–66.
7. Smith SA. Pupil function: tests and disorders. In: Bannister R, Mathias CJ, editors. *Autonomic failure*, 3rd edn. Oxford: Oxford University Press, 1992;393–412.
8. Loewenfeld IE. Age changes in pupillary diameter and reactions. In: Thompson SH, Daroff R, Frisen L, Glaser JS, Saunders MD, editors. *Topics in neuro-ophthalmology*, Baltimore: Williams & Wilkins, 1979;124–50.
9. Smith SA, Dewhirst RR. A simple diagnostic test for pupillary abnormality in diabetic autonomic neuropathy. *Diabetic Med* 1986;**3**:38–41.
10. Loewenfeld IE. *The pupil.* Detroit: Iowa State University Press/Amos Wayne State University Press, 1993; 407–79, 498–517, 1131–87, 1200–3.
11. Bourne PR, Smith SA, Smith SE. Dynamics of the light reflex and the influence of age on the human pupil measured by television pupillometry. *J Physiol* 1979; **293**:1P.
12. Ohte A, Utsumi T, Sugiyama T, Shimamura I. A re-evaluation of normal values of pupillary light reflexes and VC/VD ratio. *Folia Ophthalmol Jpn* 1994;**45**:398–401.
13. Nisida I, Ocada H, Nacano O. The activity of the cilio-spinal centers and their inhibition in pupillary light reflex. *Jpn J Physiol* 1960;**10**:73–84.
14. Smith JD, Ichinose LY, Masek GA, Watanabe T, Stark L. Midbrain single units correlating with single response to light. *Science* 1968;**162**:1302–3.
15. Sillito AM, Zbrozyna AW. The localization of the pupilloconstrictor functions within the mid-brain of the cat. *J Physiol (Lond)* 1970;**211**:461–77.
16. Theofilopoulos N, Longmore J, Kerr FA, Szabadi E, Bradshaw CM. Consensual pupillary responses to mydriatic and miotic drugs. *Br J Clin Pharmacol* 1988;**26**:697–702.

17. Morley MJ, Bradshaw CM, Szabadi E. Effects of clonidine and yohimbine on the pupillary light reflex and carbachol-evoked sweating in healthy volunteers. *Br J Clin Pharmacol* 1991;**31**:90–101.
18. Loewenfeld IE, Newsome DA. Iris mechanics: I. Influence of pupil size on dynamics of pupillary movements. *Am J Ophthalmol* 1971;**71**:347–62.
19. Szabadi E. The influence of the baseline on the size of pharmacological responses: a theoretical model. *Br J Pharmacol* 1977;**61**:492–3P.
20. Longmore J, Theophilopoulos N, Szabadi E, Bradshaw CM. Modification of the pupillary light reflex by miotic and mydriatic drugs: applicability of model of functional interaction. *Br J Clin Pharmacol* 1987;**23**:610–11P.
21. Matjucha ICA, Katz B. Neuro-ophthalmology of aging. In: Albert ML, Knoefel JE, editors. *Clinical neurology of aging*. New York: Oxford University Press, 1994;421–47.
22. Bos JE, Fock JM, Reulen JPH, Van Lith GHM. Pupil constriction and visual evoked potential latency in optic neuritis. *Neuro-ophthalmology* 1990;**10**:187–96.
23. Korszyn AD, Netanel L, Nemet P. Sympathetic pupillary tone in old age. *Arch Ophthalmol* 1976;**94**:1905–6.
24. Smith SA, Smith SE. Evidence for a neuropathic aetiology in the small pupil of diabetes mellitus. *Br J Ophthalmol* 1983;**67**:89–93.
25. Thompson HS. Diagnosing Horner's syndrome. *Trans Am Acad Ophthalmol Otolaryngol* 1977;**83**:840–8.
26. Maloney WF, Younge BR, Moyer NJ. Evaluation of the causes and accuracy of pharmacologic localization in Horner's syndrome. *Am J Ophthalmol* 1980;**90**:394–402.
27. Cremer SA, Thompson HS, Digre KB, Kardon RH. Hydroxyamphetamine mydriasis in Horner's syndrome. *Am J Ophthalmol* 1990;**110**:71–6.
28. Meller J. Ueber hyaline Degeneration des Pupillarrandes. *Von Graefes Arch Ophthalmol* 1904;**59**:221–8.
29. Pagani M, *et al.* Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 1986;**59**:178–93.
30. Strehler B, Hirsch G, Gusseck D, Johnson R, Bick M. Codon-restriction theory of aging and development. *J Theor Biol* 1971;**33**:429–74.
31. Hayflick L. The cell biology of human aging. *Sci Am* 1980;**242**:58–65.

Authors' addresses
P. Bitsios, E. Szabadi*
Department of Psychiatry, University of Nottingham,
Queen's Medical Centre,
Nottingham NG7 2UH

R. Prettyman
Department of Psychiatry, Division of Old Age Psychiatry,
University of Leicester, The Bennion Centre,
Groby Road, Leicester LE3 9DZ
(formerly Department of Health Care of the Elderly,
University of Nottingham,
Queen's Medical Centre,
Nottingham NG7 2UH)

*Address correspondence to Professor E. Szabadi

Received in revised form 23 July 1996