Autonomic insufficiency in pupillary and cardiovascular systems in Parkinson’s disease

Samay Jain a, c, *, Greg J. Siegle a, Chen Gu a, Charity G. Moore a, Larry S. Ivanco a, J. Richard Jennings a, Stuart R. Steinhauer a, b, Stephanie Studenski a, J. Timothy Greenamyre a, b, c

a University of Pittsburgh School of Medicine, PA, USA
b VA Pittsburgh Healthcare System, PA, USA
c Pittsburgh Institute for Neurodegenerative Diseases, PA, USA

Abstract

Background: In Parkinson’s disease (PD), neurodegenerative changes have been observed in autonomic pathways involving multiple organ systems. We explore pupillary and cardiac autonomic measures as physiological manifestations of PD neurodegeneration.

Methods: Pupil measures (pupillary unrest (spontaneous changes of pupil diameter in darkness), constriction velocity and redilation velocity) were assessed in 35 participants (17 PD, 18 controls). Simultaneous cardiac measures (respiratory sinus arrhythmia during deep breathing, Valsalva ratio, resting heart rate variability (HRV), orthostatic change in blood pressure and orthostatic change in heart rate) were obtained. Nonparametric statistics were used to compare PD with control participants and to calculate correlation coefficients between pupillary and cardiac measures.

Results: Pupillary unrest and orthostatic decreases in systolic blood pressure were greater in PD than controls. Respiratory sinus arrhythmia during deep breathing and resting HRV were lower in PD. Among all participants, there was a negative correlation between HRV and redilation velocity and a positive correlation between orthostatic change in heart rate and pupillary unrest. A modifying effect of PD was found on the association between high frequency HRV and pupillary unrest.

Conclusions: Results demonstrate simultaneous autonomic dysfunction in both pupillary and cardiovascular systems in PD. The correlations between pupillary and cardiac measures suggest shared central centers of autonomic integration, while the modifying effect of PD may reflect autonomic effects of PD-related pathology not present in controls.

1. Introduction

Parkinson’s disease (PD) neuropathology suggests neurodegenerative changes involve neurons in autonomic pathways affecting multiple organ systems [1] which may lead to widespread changes in autonomic physiology which if quantified may serve as non-motor markers of PD. Such markers could allow earlier diagnosis and better treatment of PD as non-motor features of PD occur earlier and contribute more to the burden of disease than do motor features [2]. Both the pupillary and cardiovascular systems may provide such physiological markers.

The pupil can provide a unique window into brain function as it integrates inputs from both cortical and subcortical structures which influence its autonomic function – parasympathetic constriction or sympathetic dilation. Pupillary measures include pupillary unrest, constriction velocity and redilation velocity. Pupillary unrest refers to spontaneous fluctuations in autonomic tone which lead to changes in pupil diameter in darkness. It is positively associated with arousal related symptoms such as sleepiness which are common in PD [3]. The cardiovascular system is also of clinical significance, as evidenced by the high prevalence of orthostatic hypotension in PD [2]. Cardiac measures include respiratory sinus arrhythmia with deep breathing, resting heart rate variability, the Valsalva ratio and orthostatic blood pressure and heart rate. Cardiac measures in PD have been reported, but mostly in isolation without taking account of how other autonomic

© 2010 Elsevier Ltd. All rights reserved.
end-organs are functioning. Our objective in this exploratory study is to simultaneously acquire measures in the pupillary and cardiovascular systems, allowing correlations of autonomic function between the two systems. Results of such analyses would reveal information on hierarchically higher centers of autonomic integration in elderly controls and how such systems may be affected in PD [4].

2. Methods

All participants were recruited from the University of Pittsburgh Medical Center. The IRB gave ethical approval and the participants signed informed consent. PD participants fulfilled the UK PD Society Brain Bank Clinical Criteria, scoring Hoehn and Yahr Stage (HY) < 5, taking either no anti-parkinsonian medication, carbido/ levodopa or dopamine agonists. As a group, controls were age and sex matched to PD participants. Exclusion criteria included: pyramidal and/or cerebellar signs, any other organic brain disorder, prior intracranial surgery, uncorrectable eyesight, bilateral cataract surgery, diabetes, uncontrolled hypertension, cardiac dysrhythmia, inability to participate due to motor disability (HY > 5), taking medications affecting autonomic measures which could not be safely withheld, history of polyneuropathy or failure to pass a toxicology screen for substances that could influence results (alcohol, opiates, cocaine, cannabis, benzodiazepines and amphetamines). Baseline measures included age, sex, HY Stage and the Unified Parkinson's Disease Rating Scale (UPDRS). All physiological assessments were conducted in a quiet room free of distracting stimuli. Session were done at the same time every morning (09:00); at the same ambient temperature (22–24 °C) in the same seated position to minimize effects of circadian variation, temperature and position on autonomic measures. At first, it was not clear medications could be safely or practically withheld so the first five participants were tested on medication. All subsequent participants withheld all dopaminergic medications and agents that would influence autonomic measures (e.g., anti-hypertensives) for at least 12 h prior to testing. Pupillary and cardiac measures at rest were obtained simultaneously in darkness. Pupillary measures included pupillary unrest, constriction velocity and redilation velocity. Pupillary unrest was assessed as in the Pupillary Sleepiness Test [3], using infrared video pupillography, which digitized measurement of the horizontal pupil diameter of one eye (SCAN RX726 sampling at 60 Hz with a resolution of 0.04 mm). Participants were seated in front of a computer monitor in darkness (illumination – 0.027 candlepower with monitor on) resting comfortably on a head and chin rest. They were instructed to stare at a dim red fixation point (intensity -0.03 cd/m2) at eye level at a distance of 28.75” subtending a visual angle of 0.25” for 11 min. Pupil constriction and redilation velocity was measured by administering the light reflex. After 3 min in darkness, 11 “flashes” (a white circle subtending a visual angle of 4.60”) were presented (1 s duration, every 10 s) at eye level at a distance of 73 cm with and intensity of 13 cd/m2. The light reflex was performed separately from cardiac measures to avoid any potential cardiac-arousing responses. Stimulus presentation was programmed with E-prime routines. ECG (modified lead II placement) was sampled at 1000 Hz utilizing Grass model 7 neuradota amplifiers. Resting ECG was recorded for 11 min during pupillography. The Valsalva ratio was measured with the Valsalva maneuver by asking participants to force expiration against a closed glottis at a pressure of 15 mmHg for 15 s. Respiratory sinus arrhythmia was measured by asking participants to take six deep breaths at a pace of 0.1 Hz, visually cued by a breathing metronome. Orthostatic blood pressure and heart rate were measured after the participant was in a supine position for 5 min, and then again after the participant had been standing for 2 min.

2.1. Signal processing

All physiological recordings were manually inspected for artifacts and proper signal processing. For pupillography, this consisted of removal of blink artifact and for ECG this consisted of removing motion artifact and confirming R-wave detection. As described by Ludtke et al. [3], pupillary unrest was quantified employing a fast Fourier transform and summing spectral power from 0 to 0.8 Hz for 82 s segments of data. Because several participants were unable to stay awake and keep their eyes open for 11 min, the pupillary unrest measure reported is the spectral power for the first 64 s of pupil signal collected. For light reflex responses, the pupil response was averaged across the last 10 trials. Constriction velocity is the maximum velocity during constriction (mm/s) and redilation velocity is the change in diameter divided by time elapsed from 50% to 75% redilation [5]. For cardiac measures, resting heart rate variability (HRV) was the spectral power of a 5 min ECG recording of two frequency bands (low: 0.04–0.15 Hz and high: 0.15–0.40 Hz) calculated using Fast Fourier Transform on interbeat (RR) intervals of a 5 min recording. Valsalva Ratio was calculated by dividing the maximum RR interval by the minimum RR interval during Valsalva and within 30 s after the maneuver. Respiratory sinus arrhythmia was the average difference between maximum and minimum heart rate during deep breathing. Orthostatic variables were the standing systolic blood pressure or heart rate subtracted from their supine values.

2.2. Statistical analysis

Wilcoxon rank-sum tests (for HRV in low and high frequency bands) or 2-sided t-tests (for all other measures) were used for comparisons between groups. Combining data from both PD and control groups, Spearman correlation coefficients were used to determine associations among pupil and cardiovascular measures. Tests for modifying the effect of PD on the correlations between each paired pupillary and cardiovascular measure were performed. Levodopa equivalent dose was calculated for each participant [6]. A secondary analysis compared those PD participants in which anti-parkinsonian medications were withheld with those in whom they were not. Analyses were performed with Stata® (StataCorp LP, version 10). Because this exploratory study is intended for planning research and hypotheses generation, an α = 0.10 was selected a priori and effect sizes (Cohen’s d (difference between group means divided by the pooled standard deviation)) were also calculated.

3. Results

Characteristics of PD and control groups are summarized in Table 1. Pupillary unrest was higher in PD and four of the six cardiovascular measures were lower in PD compared to controls. Medications in the first five participants were not withheld and included: no medications in the first participant; selegiline 5 mg/day and levodopa 800 mg/day in the second; amantadine 200 mg/day and ropinirole 12 mg/day in the third; levodopa 600 mg/day in the fourth; and levodopa 300 mg/day in the fifth. There were no significant differences in any outcome measure between the PD participants in which anti-parkinsonian medications were withheld vs. those in which they were not with the exception of redilation velocity (0.37 (0.05) vs. 0.25 (0.04) mm/s, respectively, (Wilcoxon rank-sum, p = 0.09)).

Significant correlations were seen between low frequency HRV and redilation velocity ($r_{s} = -0.35$), high frequency HRV and redilation velocity ($r_{s} = -0.36$), and orthostatic heart rate and pupillary unrest ($r_{s} = 0.34$). One correlation demonstrated a significant modifying effect by PD: the correlation between high frequency HRV and pupillary unrest was lower in PD than in controls ($r_{s} = 0.19$ vs. 0.51). Because combining data from both groups for correlations may introduce bias, we conducted a supplementary analysis looking at correlations within each group. The three significant correlations were in the same direction within each group and no significant differences were seen between PD and controls.

4. Discussion

Simultaneous recordings of pupillary and cardiovascular autonomic measures in PD have not been previously reported. We observed lower HRV in both low and high frequency bands, greater decreases in supine to standing (orthostatic) systolic blood pressure and higher pupillary unrest in PD relative to controls. This represents lower sympathetic and parasympathetic cardiac function, as well as higher autonomic variability in pupillary function in PD.

Given the known association of pupillary unrest with sleepiness, the observation of higher pupillary unrest in PD is consistent with the fact that disorders of arousal such as daytime sleepiness and REM sleep behavior disorder are common in PD [2]. To distinguish parasympathetic from sympathetic function in the pupil, we conducted the light reflex. When the pupil is exposed to a brief light stimulus, it constricts and then redilates. The measure of constriction velocity is parasympathetic while the latter portion of redilation (after initial parasympathetic withdrawal) is sympathetic. We did not find lower pupil constriction velocity in PD as reported by others [7]. This could be because our light stimulus was of longer duration or that our PD population limited in severity (mean Hoehn and Yahr stage = 1.7) compared to other studies. We
know of no previous reports of redilation velocity in PD, which was not significantly different when compared to controls. Five participants taking anti-parkinsonian medications had lower redilation velocities than PD participants in which such agents were withheld, suggesting possible sympathetic withdrawal secondary to medication. This interpretation is limited, however, as data from these same participants off anti-parkinsonian agents is not available.

Our findings of cardiovascular autonomic dysfunction PD is consistent with other studies [8,9]. Specifically, lower resting HRV in high frequency bands indicates lower parasympathetic function, while lower resting HRV in low frequency bands typically reflects lower sympathetic and parasympathetic function [10]. The greater reduction in orthostatic blood pressure along with the lower HRV in high and low frequency bands in PD are consistent with lower sympathetic and parasympathetic cardiac function, respectively.

The simultaneous acquisition of cardiovascular and pupillary measures allowed us to see if autonomic function from the two organ systems correlate with one another, revealing information on centers of autonomic integration in elderly controls and how such systems may be affected in PD. Among all participants, we found that HRV in both high and low frequency bands negatively correlates with pupillary redilation velocity. Furthermore, orthostatic change in heart rate positively correlates with pupillary unrest. This indicates involvement of either central autonomic networks which in species and descending peripheral autonomic pathways are affected in PD. A modifying effect of PD on the correlation between high frequency HRV and pupillary unrest was observed which may reflect autonomic effects of PD-related pathology not present in controls.

Due to the small number of participants, we were unable to determine if Parkinsonian motor signs (UPDRS-III) correlated with autonomic measures, though another study found HRV to be negatively correlated with severity of Parkinsonism [9]. Participants were also limited in their range of PD severity. It is possible that with more participants or more advance stage PD, we would detect more differences in autonomic function between PD and controls, more associations among cardiac and pupillary autonomic measures, or more modifying effects of PD. Although medications were withheld for at least 12 h, residual effects of longer acting measures, or more modifying effects of PD. Although medications were withheld for at least 12 h, residual effects of longer acting dopamine agonists may have still been present. Despite these limitations, this exploratory study establishes the feasibility of novel autonomic measures acquired simultaneously in multiple organ systems and illustrates how such studies can provide insight to our understanding of pathophysiology in PD. Understanding mechanisms of autonomic dysfunction will aid in the development treatments for dysautonomia in PD. Additional studies are underway to relate autonomic changes with motor signs in PD in an effort to determine if autonomic physiology can be utilized as a non-motor marker of progression in PD.

Acknowledgments

NIH grants KL2 RR024154, KMH082998, MH55762, P30 AG-024826, UL1 RR024153, Dept. of Veterans Affairs, and the American Parkinson’s Disease Association Center for Advanced Research at the University of Pittsburgh.
References