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SHORT COMMUNICATION

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Pupillary light reflex in panic disorder

A trial using audiovisual stimulation

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Abstract *Background* Although many previous studies reported abnormalities of autonomic function in patients with panic disorder (PD), almost all targets in those studies primarily focused on cardiovascular autonomic functions. In the present study, we determined whether PD patients exhibited abnormalities in the pupillary autonomic nervous system (ANS). *Methods* Before and after audiovisual stimulation (AS), which induced mental stress through exposure to video images of high stress experiences, such as driving motor vehicles, the pupillary light reflex (PLR) was measured by infrared pupillometer in 13 remitted PD patients and twenty age- and gender-matched normal controls (NC). *Results* Before and after AS, there were no significant differences in initial pupillary diameters in dark conditions (D1), pupillary diameters at maximum constriction (D2) or constriction ratios (CR: (D1-D2)/D1) between PD and NC subjects. However, the CR ratio (CR before/CR after) was significantly higher in the PD group than in the NC. *Conclusions* These findings suggest that even remitted PD patients may have a dysfunctional PLR regulation with experimental stressors such as AS.

Key words autonomic function · sympathetic · parasympathetic · pupil · remission

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Introduction

Many researchers have focused on the sympathetic nervous system (SNS) in PD, especially the autonomic nervous system (ANS) that regulates the cardiovascular system (see reviews; Jeejeebhoy et al. 2000) since PD patients exhibit a high frequency of cardiovascular symptoms (Margraf et al. 1987; Shioiri et al. 1996). However, no consistent ANS abnormality in PD patients has been uncovered to date (see reviews; Jeejeebhoy et al. 2000).

The human pupil is eminently suitable for studying the relationship between sympathetic and parasympathetic activity in human subjects (Bitsios et al. 1996). In particular, attenuation of the reflex response is a useful indicator of subtle lesions to autonomic nerves (Smith 1992; Bitsios et al. 1996). It is also suggested that the PLR response is more sensitive in detecting ANS abnormalities than ECG analysis (Shirakawa et al. 1991; Yoshitomi et al. 1999). In addition, the relationship between PLR and anxiety is well established (Loewenfeld 1993). More recently, two separate researchers suggested a significant correlation between state/trait anxiety and the PLR amplitude, the initial pupillary diameter, and the PLR constricted diameter in healthy subjects (Bitsios et al. 2002; Nagai et al. 2002).

In the present study, we tested remitted PD patients only, and compared their PLR functions to normal control subjects. We hypothesized that there might be some abnormalities of PLR function during periods of remission in patients with PD.

Subjects and methods

Subjects

The subjects were 13 male out-patients (mean ± SD age, 34.1 ± 8.4 years) who had been diagnosed with PD according to DSM-IV criteria (American Psychiatric Association 1994). None of the patients had any comorbidity of depression, and all were examined after they had

received 2 or 3 years of treatment and were in the PD remission phase, defined as the absence of agoraphobia and major panic attack symptoms, for at least 6 months preceding the PLR measurement. All were receiving regular outpatient treatment, including medication. None were found to have any past head injuries, neurological disorders, drug or alcohol abuse, or serious medical illnesses. Only five patients (38%) were treated with the serotonin paroxetine (10–40 mg/day) or fluvoxamine (50–150 mg/day) and all patients had not taken any benzodiazepines for at least a month before the examination.

Twenty mentally and physically healthy control subjects (NC; 34.4 ± 9.0 years), who were age and gender matched with individual PD patients, were selected from among a group of volunteers. All control subjects were in good physical health and none had any notable history of mental disorder, neurological disease, head injury, or substance dependence, nor had any family history of mental disorder or substance dependence.

The psychiatric state of each patient on the examination day was assessed immediately before the PLR measurement using the patients-rated Sheehan Anxiety Scale (SAS; Sheehan 1986).

Audiovisual stimulation (AS)

In this study, we used AS as a mental load that included psychological stress, which changes autonomic nervous activity and may occasionally cause dizziness or any kind of distress. Subjects were exposed to video images taken by camera on motor vehicles such as karts, cars, and so on, for 17 minutes. In the middle of the video playback, the subjects watched a tropical sea scene for 40 seconds to relax. Before and after loading the AS, each subject rested for 5 minutes. The AS method was basically similar to that described previously (Kojima et al. 2002). This study was approved by the ethical committee of Niigata University Graduate School of Medical and Dental Sciences.

Measurements and data analysis

Pupil diameter was measured in the dark before and after the AS using an infrared pupillometer (Iriscorder C7364, Hamamatsu Photonics, Japan) in which a charge-coupled device (CCD) camera (with an effective field of 30 x 22.5 mm) took an image of the pupil at a sampling time of 1/60 s (the field was illuminated by a light-emitting diode (LED) with a peak wavelength of 890 nm). Another LED in the pupillometer (peak wavelength, 660 nm; maximum intensity, 10μW) was lit for 1 second to induce a PLR response. The baseline pupil diameter was measured after subjects had at least 5 min of rest in the dark (luminance, 10 lx).

PLR amplitude is dependent on the initial pupillary diameter in the dark before light stimulation (D1). We then adopted a constriction ratio (CR) (Hasegawa and Ishikawa 1989) to balance the differences in D1 as follows: CR = (D1–D2)/D1, where D2 is the pupillary diameter at maximum constriction at the light reflex peak. To evaluate the differences between CR before and CR after, we also defined the CR ratio as follows: CR ratio = CRafter/CRbefore, where CRbefore and CRafter are the CRs measured before and after AS, respectively. In addition, to evaluate the absolute changes in the CR, we also defined the CR factor as follows: CR factor = abs {1 – (CRafter/CRbefore)}. The symbol abs {x} indicates the absolute value of x.

An 11^{th}-power polynominal curve was fitted to the rising or falling time course of the PLR response (MATLAB software, ver 5.2, Math Works, USA). The maximal velocity and acceleration of pupillary constriction and the maximal pupil redilation velocity during light reflex response were calculated by first- and second-order fitted curve differentiation.

Statistical analysis

As for statistical analysis, we used a Kolmogorov-Smirnov test and a Pearson's correlation coefficient. Values were expressed as means ± S. D. A probability level of $P < 0.05$ was regarded as statistically significant. The data were analyzed using statistical SPSS software (release 10.07J, SPSS).

Results

There was a significant group difference in SAS (PD group: 64.6 ± 19.9, NC group: 36.5 ± 2.8, $t = 3.97$, $p < 0.002$), but not in age or gender. No subject in either group experienced panic symptoms during AS or noted a dislike for the AS, by saying, for example, that they would "never try it again."

Fig. 1 shows the differences in the CR ratio and CR factor between the PD and NC groups. Both parameters in the PD group were significantly higher than those in the NC group ($p < 0.03$, $p < 0.02$, respectively). There was a significant correlation between SAS total scores and the CR ratio ($r = 0.48$, $p = 0.017$) in all subjects, but we found an especially strong correlation in the PD group ($r = 0.75$, $p < 0.01$). The PLR parameters were not significantly correlated with age at PD onset, duration of illness, or medication.

Discussion

Abnormalities in the PLR function of PD patients after mental loading are of great interest since panic symptoms, including panic attack (PA), are involved in cardiovascular symptoms, but not pupillary ones (Margraf

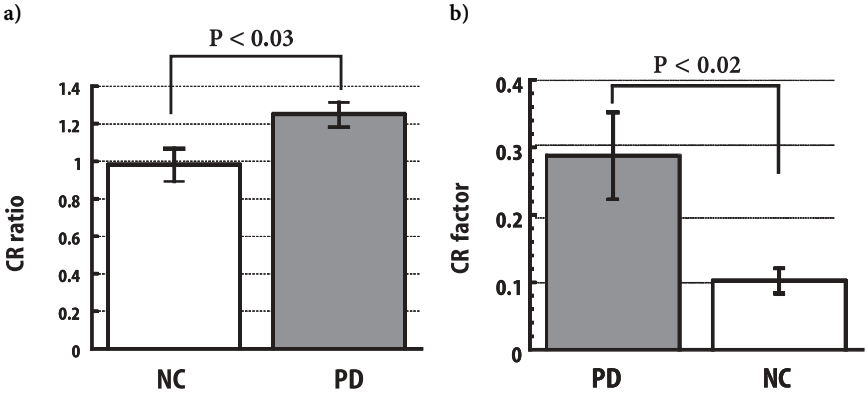

Fig. 1 CR ratio and CR factor in the PD and NC groups. **a** CR ratio in both groups. The CR ratio in PD subjects was significantly higher than that in the NC subjects ($z = 2.56$, $p < 0.03$). **b** CR factor in the two groups. There was a significant difference in the CR factor between the groups ($z = 2.89$, $p < 0.02$)

et al. 1987; Shioiri et al. 1996). Indeed, pupillary symptoms are not listed in the DSM-IV PD diagnostic criteria (American Psychiatric Association 1994). However, some panic symptoms such as derealization, fear of losing control and fear of dying during a PA may be relevant to pupillary function because of significant correlations between fear/anxiety and the PLR (Bitsios et al. 1996, 2002).

Miotic response abnormalities evoked by brief light stimuli are mediated mainly by the parasympathetic effect or fibers, and the latency and amplitude of this response have been used as indices of parasympathetic functioning (Smith 1992). On the other hand, the response recovery phase is believed to have a sympathetic component since adrenergic neuron blocking drugs can delay recovery of the baseline pupil diameter following light stimulation (Smith 1992; Loewenfeld 1993). Therefore, it is possible that, even in remitted PD patients, there may be subtle parasympathetic dysfunctions which are hypersensitive to and are rendered unstable by mild stress such as AS.

Another possible explanation for PLR abnormality in PD patients may lie in the influence of higher centers on the Edinger-Westphal nucleus via the hypothalamus and/or amygdala (Bakes et al. 1990). There is an anatomical/physiological link between the amygdala and midbrain pupillomotor center (Edinger-Westphal nucleus) (Bitsios et al. 1996). The hypothalamus receives afferent input from the central nucleus of the amygdala (LeDoux et al. 1988), and there is a well-documented inhibitory projection from the posterior hypothalamus to the Edinger-Westphal nucleus (Bitsios et al. 1996). Recently, the fear network from the level of the amygdala through its projects to the hypothalamus and the brainstem is noteworthy for the neuroanatomical basis of PD (Gorman et al. 2000). Thus, our findings concerning PLR may be due to amygdala dysfunction in PD patients. Further studies are needed.

In conclusion, using this new method, we found a dysfunctional PLR regulation in remitted PD patients. It is suggested that this new technical approach may be used to measure the autonomic function in other psychiatric disorders such as post-traumatic stress disorder (PTSD), GAD, social anxiety disorder, specific phobias, and depression.

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