Electroretinogram B-Wave Amplitude in Panic Disorder

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ABSTRACT

Abnormal light-related behaviors have been described for patients with panic disorder (PD). The present study was undertaken to investigate the retinal light response in PD using electroretinography (ERG). The authors conducted b-wave ERG measurements with a bright light (after dark adaptation) in 28 patients with PD and 28 control subjects. There were no significant differences in the mean b-wave amplitude between the two groups, but the retinal response to light in PD patients was generally lower than in healthy subjects. A large interindividual variability was found; also noted was a significant difference in the mean b-wave amplitude between the right and left eyes in the control group. The data indicate subtle variation of retinal photosensitivity in a subgroup of patients with PD. Because dopaminergic retinal activity affects b-ERG amplitude, the authors hypothesize that the dopaminergic system is involved in the response to light in PD patients.

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INTRODUCTION

Excessive light sensitivity is a feature of psychiatric illness (eg, schizophrenia, bipolar disorder, and winter depression).[1-3] A relationship between light exposure and panic disorder (PD) has been documented recently. Most PD patients are sensitive to increased environmental light and frequently show light-related avoidance behaviors.[4] The onset and exacerbation of panic attacks (PA) are more common in the summer.[5] In most patients, the first PA occurs between 6AM and 6PM.[6] Pulsating fluorescent light increases anxiety and elicits somatic symptoms prodromal to PA[7,8]; however, the link between light exposure and the exacerbation of PA remains unclear. It is possible that the mechanism of sensitivity to light in PD involves the retina, either directly or indirectly.

In the present study, we examine retinal photosensitivity in PD and healthy subjects by means of electroretinography (ERG). ERG measures the electrical response of the retina to standardized light stimuli during dark or light adaptation.[9,10] The ERG parameters include amplitude, waveform (a-, b-, and c-wave), and implicit time (time from stimulus onset to the peak of waveform). When the intensity and chromatic characteristics of the light stimulus are varied, the ERG can indirectly assess rod, cone, or mixed rod/cone photoreceptor function to provide an objective measure of retinal sensitivity to light.[11] In particular, the a-wave negative is the first to appear following the stimulation of light and has been linked to electrical activity of the external segment of the photoreceptors.[12]

On the contrary, the c-wave is related to electrical activity of the pigmented epithelium.[13] However, this latter morphologic element is not reported in the ERG habitually drawn from humans because of its modest clinical significance and the availability of other methods to survey the activity of the pigmented epithelium, such as electro-oculography.

The b-wave reflects the activity of the inner nuclear layer, whose bipolar cells are in synaptic connection with the interplexiform dopaminergic neurons.[14,15] Several research studies on healthy volunteers confirmed this hypothesis, showing variations of b-wave activity after the administration of the agonist and antagonist of dopaminergic transmission. Thioridazine[16] and perphenazine[17] can reduce b-wave amplitude, whereas carbidopa and levodopa[18] and bromocriptine[17] cause an increase in b-wave amplitude.

As far as the receptors are concerned, diverse types of dopamine receptors have been identified in all the retinal cells.[19] Dopamine effects vary between different retinal cell types, most likely owing to differences in cell-specific receptor subtype expression.[20] Dopamine D_1 receptors are most heavily expressed in processes stratifying in the plexiform layer beginning at birth.[21] In goldfish retina, D_1 receptor immunoreactivity is more intense over amacrine cells in the proximal inner nuclear layer and bipolar cells in the distal inner nuclear layer. The Muller cells and axons of cone photoreceptors are labeled as well.[22]

The D_1 B-receptor has a possible role in modulating phagocytosis by the pigment epithelium; dopamine uncouples the horizontal and amacrine cell-gap junction through a D_1-like receptor.[19] The D_2 R-receptor immunoreactivity also was seen throughout the inner plexiform layer, mainly on intracellular vesicles, whereas the immunoreactivity associated with the plasma membrane was always extrasynaptic; these findings indicate that D_2-like responses are mediated through the D_2 R subtype by an autoreceptor mechanism in

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dopaminergic cells, and by volume transmission in nondopaminergic cells of the inner retina.[20] The D_4 receptor likely is involved in the inhibition of melatonin synthesis in the photoreceptors.[19]

Retinal dopamine receptor distribution is more extensive than dopamine neuron innervation, but the distribution is consistent with physiologic estimates of dopamine function, suggestive of both wiring and volume transmission of dopamine in the retina.[22] The observation of Kramer[23] in 1971 allowed formulation of the hypothesis of a dopamine release after a stimulation of light.

The role of the retinal dopaminergic neurons in visual function is not clear. Perhaps the neurons are involved in the process of adaptation[24]; in fact, animals which have less dopaminergic interplexiform cells show a visual defect in terms of light sensitivity.[25]

Previous applications in psychiatry (eg, seasonal affective disorder,[26] schizophrenia,[27] and cocaine dependency[28]) have suggested that ERG can be used to evaluate sensitivity to light mediated by retinal dopaminergic activity.

MATERIALS AND METHODS

Subjects

Twenty-eight patients (17 female and 11 male; mean age, 29.8 years; SD, 13.33; age range, 18–46 years) were recruited at the Department of Psychiatry, University of Siena, Italy. They met the criteria of PD as described in the *Diagnostic and Statistical Manual of Mental Disorders*,[29] Third Edition-Revised (*DSM-III-R*) on the basis of the Structured Clinical Interview for the *DSM-III-R*–Patient Edition (*DSM-III-R*–SCID-P).[30] The exclusion criteria were intra-episodic and lifetime psychiatric comorbidity. The patients were either unmedicated or medication-free for at least 3 weeks prior to enrollment. In addition, a group of sex- and age-matched control subjects (n=28 [17 female and 11 male]; mean age, 30 years; SD, 15.04; age 18–46 years) were recruited. They were assessed as being free of mental disorders on the basis of the Structured Clinical Interview for the *DSM-III-R*–Non-Patient Edition (*DSM-III-R*-SCID-NP). None of the patients reported taking psychoactive drugs.

The patients and controls were free of all major medical disorders. Written informed consent was obtained from the psychiatric and healthy subjects after an explanation of the study procedures that had been approved by the Ethics Committee of Siena University. On the basis of personal history and clinical interview, we made sure all subjects were able to give informed consent.

Electroretinography Measurements

The morning of the study, each subject was again informed of all procedures. It was explained that some people experience anxiety and/or discomfort during the ERG recording, but that such feelings are always transient and not dangerous in any way.

All participants received a clinical ophthalmologic evaluation consisting of standardized visual acuity and bilateral fundus examinations.

A standardized measure of anxiety was not obtained during the testing day because data on possible b-wave variations in a generally stressful situation are contrasting, and a particular trend of the b-wave in performance

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TABLE. B-WAVE AMPLITUDE OF RIGHT EYE (RE) AND LEFT EYE (LE) IN PATIENTS WITH PANIC DISORDER (PD) AND HEALTHY SUBJECTS

Amplitude Measured	Patients With PD (n=28)	Healthy Subjects (n=28)
RE	66.23	68.14
LE	67.13	72.61
Mean between RE and LE	66.68	70.37

The two-tailed *t*-test was used for all comparisons.
RE in healthy subjects vs RE in PD patients (unpaired *t*-test): t=0.41, df=55, P=0.68
LE in healthy subjects vs LE in PD patients (unpaired *t*-test): t=1.15, df=54, P=0.26
RE vs LE in PD patients (paired *t*-test): t=-2.05, df=27, P=0.53
RE vs LE in healthy subjects (paired *t*-test): t=-2.05, df=27, P=0.032
PD patients vs healthy subjects (unpaired *t*-test): t=2, df=54, P=0.42

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anxiety has not been demonstrated.[31] However, all participants were considered, by the psychiatrist who accompanied them, as psychologically able to undergo testing.

ERG recordings were performed between 9AM and 12PM. All subjects were tested after 30 minutes of dark adaptation. The pupils were dilated using tropicamide 1% with phenylephrine. Two cutaneous electrodes (noninvasive technique) were placed under the border of the lower eyelashes. The ground electrode was placed on the back of the left hand. The ERG signal was obtained in response to single flashes of white light presented as computerized stimuli in a large ganzfeld box surrounding the subject's head. A series of 10 flashes was presented at 30-second intervals and repeated at each of the following intensities: 1 candle/m^2 and a signal bandwidth of 1 Hz. ERG signals were recorded with an EREV-2000 system (Lace Electronic, Pisa) as two waveforms (right and left eyes). The b-wave amplitude was measured from the trough of the a-wave to the peak of the b-wave and expressed in microvolts. For each subject, we calculated the mean of the measurements obtained after 10 flashes. The two-tailed Student's *t*-test was performed to compare the mean b-wave amplitude of the right and left eyes in each group. Women and men also were compared.

"Because no data is available on the ERG in healthy subjects or on physiologic differences between the left and right eyes, it is not possible to explain the significance of the left/right-eye discrepancy."

RESULTS

The mean b-wave amplitude of patients with PD was lower than that of control subjects, but the difference was not significant (Table). In two patients, the ERG recording was stopped early because of increased anxiety and the elicitation of somatic symptoms prodromal to PA. There was no significant difference between women and men in either the PD group (t=2.01, df=26, P=0.36) or the control group (t=1.8, df=26, P=0.64). No significant correlation was found between b-wave amplitude and age in the PD patients (r=0.15) or control subjects (r=0.04). We did observe the following: (1) a large inter-individual variability of b-wave amplitude (control subjects: mean±SD=70.34±14.19; PD patients: mean±SD=66.68±18.75); (2) a significant difference in mean b-wave amplitude between right (<) and left (>) eyes in control subjects; and (3) no significant difference in b-wave amplitude between the right and left eyes of the PD patients (Table).

DISCUSSION

The ERG recording had to be stopped early in two female patients (7%) because of the onset of severe anxiety symptoms; this confirms the sensitivity to the anxiogenic power of light stimulation.[7,8] Although there was no statistically significant difference in b-wave amplitude between the PD patients and the control subjects, probably owing to the relatively small sample, the retinal activity in the first group showed lower values than that in the second group.

There was a significant difference in b-wave amplitude between the right and left eyes of healthy subjects but not of PD subjects. Because no data is available on the ERG in healthy subjects or on physiologic differences between the left and right eyes, it is not possible to explain the significance of the left/right-eye discrepancy. This has not even been studied in the field of ophthalmology. Nevertheless, the lack of difference between the left and right eyes of PD subjects may indicate that anxiety states annul this "normal" asymmetry probably because of an abnormal retinal response to light in PD. This peculiar photosensitivity of the retina may be caused by a dysfunction of the retinal dopamine system (ie, the recorded activity is supposed to correlate with the central activity of dopaminergic neurons).[15] In fact, since the retina and central nervous system have common embryologic origins and several structural and functional similarities, the ERG may provide valid information about central dopaminergic activity.[18]

CONCLUSIONS

The findings of this study suggest a role of the dopamine system in some aspects of PD, as already reported. Cholecystokinine tetrapeptide, which in healthy subjects induces symptoms similar to those of panic attacks, increases peripheral concentrations of norepinephrine, epinephrine, and dopamine in both plasma and platelets.[32] Cocaine abusers may show panic-related emotional disturbances.[33] The admnistration of levodopa in patients with Parkinson's disease may lead to the development of a number of psychiatric symptoms, including panic attacks,[34] even if one cannot extrapolate neurobiologic mechanisms from such observations alone. It is interesting that many compounds with dopaminergic action produce panic-like symptoms. Moreover, a genetic study suggests

that a polymorphism of the D_4 receptor and the dopamine transporter may be related to PD.[35] Although the role of dopamine in the pathophysiology of PD is not clearly established and needs to be investigated more thoroughly, we believe that the study of ERG activity may constitute a fruitful peripheral tool in this area. CNS

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