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Impact of blue vs red light on retinal response of patients with seasonal affective disorder and healthy controls

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ABSTRACT

Objectives: Seasonal affective disorder (SAD) is characterized by a mood lowering in autumn and/or winter followed by spontaneous remission in spring or summer. Bright light (BL) is recognized as the treatment of choice for individuals affected with this disease. It was speculated that BL acts on photosensitive retinal ganglion cells, particularly sensitive to blue light, which led to the emergence of apparatus enriched with blue light. However, blue light is more at risk to cause retinal damage. In addition, we reported using electroretinography (ERG) that a 60 min exposure of BL could reduce rod sensitivity. The goal of the present study was to verify if this decreased in sensitivity could be a consequence of the blue light portion present in the white light therapy lamps. We also wanted to assess the effect of monochromatic blue light vs red light in both healthy controls and patients with SAD.
Method: 10 healthy subjects and 10 patients with SAD were exposed in a random order for 60 min to two different light colors (red or blue) separated by an interval of at least 1 day. Cone and rod ERG luminance-response function was assessed after light exposure.
Results: A two-way ANOVA indicates that blue light decreases the maximal ERG response (Vmax) in both groups in photopic ($p<0.05$) and scotopic conditions ($p<0.01$).
Conclusion: The main finding of this experiment is that blue light reduces photoreceptor responses after only a single administration. This brings important concerns with regard to blue-enriched light therapy lamps used to treat SAD symptoms and other disorders.

1. Introduction

Seasonal affective disorder (SAD) is a syndrome characterized by a mood lowering in autumn and/or winter followed by a spontaneous remission in spring or summer (Rosenthal et al., 1984). In the DSM-IV, SAD is classified as a subset of recurrent major depression with seasonal pattern (DSM-IVR). But in contrast to typical symptoms of decreased appetite and insomnia usually observed in major depression, SAD patients tend to demonstrate more atypical symptoms such as hyperphagia and hypersomnia (Partonen and Rosenthal, 2001). The origin of SAD remains unknown, although it is recognized that the mood and symptom fluctuations seem to be linked to seasonal change in the photoperiod. In fact, the decrease in light exposure during fall and winter has been hypothesized to trigger SAD whereas the increase of light exposure during spring and summer was hypothesized to prompt the remission. Consequently, administration of bright light (BL) was proposed and recognized as the treatment of choice for individuals affected with SAD based on well documented therapeutic efficacy (Eastman et al., 1998; Golden et al., 2005; Lam et al., 1997; Terman et al., 1998). Currently, the recommendation for bright light therapy consists in a daily exposure to an artificial white light source of 10,000 lx for about half an hour, preferably in the morning (DBT, 2009). This particular treatment has been shown to be as effective as antidepressants to alleviate depressive symptoms (Partonen and Lonnqvist, 1996) with the advantage of avoiding medication.

The way BL acts to alleviate SAD symptoms is unknown. But the discovery of a third class of photoreceptor called «intrinsically photosensitive retinal ganglion cells» (ipRGC) has generated a new knowledge about circadian physiology which may have some implication in our understanding of some circadian disorders and their treatments, such as light therapy in SAD (Terman, 2009). Indeed, ipRGC contain melanopsin, a photopigment that is highly sensitive to blue wavelengths (Gamlin et al., 2007). Moreover, this system appears to be specialized in ambient light irradiance measurement and non-image forming photoreception (Bailes and Lucas, 2010). The discovery of melanopsin has triggered considerable interest in blue

Abbreviations: BL, bright light; ERG, electroretinogram; SAD, seasonal affective disorder.

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light by scientists as well as manufacturers. Blue light devices are growing in popularity and this is not without fundament since recently a missense variant of the melanopsin gene was found in patients with SAD, indicating that melanopsin variants may predispose some individuals to this pathology (Roecklein et al., 2009).

While on the one hand, ophthalmologic exams revealed no damage to the eyes even after years of use of conventional white BL therapy (Gallin et al., 1995), blue light on the other hand, is more at risk to cause retinal damage, a phenomenon referred to as the blue light hazard. For example, it was shown that a 470 nm exposure (at a retinal irradiance of 46 mW/cm^2) could cause extensive damages to both photoreceptors and retinal pigment epithelium (RPE) (Gorgels and van Norren, 1995), meaning that blue light alters different cellular layers of the retina. Adding to the fact that in the recent years, the use of BL has been extended to other pathologies (as adjunctive therapy) such as: major depression (Even et al., 2008; Martiny et al., 2005; McEnany and Lee, 2005), bipolar depression (Sit et al., 2007) ante- and post-partum depression (Corral et al., 2000; Oren et al., 2002), premenstrual syndrome(Lam et al., 1999; Parry et al., 1993), sleep disorders (Gooley, 2008), obesity (Dunai et al., 2007), eating disorders (Braun et al., 1999; Lam et al., 1994; Yamamotova et al., 2008), Parkinson disease (Willis and Turner, 2007), attention-deficit/hyperactivity disorder (Rybak et al., 2006) and even in Alzheimer patients with severely impaired rest–activity rhythms (Dowling et al., 2005), it becomes important to further investigate the impact of blue light on the retina.

In fact, we recently reported, using electroretinography (ERG) to assess retinal functioning, that a 60 min exposure of BL of 10,000 lx originating from a standard commercial light therapy device could reduce rods sensitivity (Gagné et al., 2007). We proposed that this reduction would be attributable to a retinal mechanism protecting the rods against bright light. However, considering the possible damaging effect of blue light, the objective of the present study was to verify if this decreased in sensitivity could be in fact the result of the blue light portion present in the bright white light therapy device used in the latter study. In addition we wanted to take advantage of the present protocol to assess, on the retina, the effect of monochromatic blue light vs red light which is far less hazardous (ACGIH, 2007) in both healthy controls and patients with SAD. In order to do so, we first measured the amount of blue vs red light present in the light therapy device that was used in our previous study to deliver 10,000 lx. We then exposed patients and healthy controls to 60 min exposure of blue light and red light on two different occasions, after which photopic (cones; day vision) and scotopic (rods; night vision) ERGs were performed. Our hypothesis was that in healthy controls a decrease in rod sensitivity would be observed in the blue light condition when compared to the red light whereas in SAD patients, who are already demonstrating some retinal function anomalies (Hebert et al., 2004; Lam et al., 1992; Lavoie et al., 2009) a different response would be observed in the presence of blue light.

2. Method

2.1. Sample

Ten patients with SAD (9 females and 1 male) aged between 22 and 36 years old (mean 28.3 SD 4.4) and 10 healthy controls aged between 20 and 36 years old (mean 28.1 SD 4.3) were recruited on the campus of Université Laval by email solicitation. All participants signed a consent form approved by the institutional ethics committee (Centre de Recherche Université Laval Robert-Giffard). The participants were matched for age and gender and none were taking medication at the time of the study, except for oral contraceptives in women. Participants with extreme chronotypes based on a French adaptation of the Morningness–Eveningness Chronotype Questionnaire were not selected.

2.1.1. SAD group

Patients were selected based on scores greater than: 13 on the French version of the Beck Depression Inventory II (BDI-II), which assesses the severity of depression; 11 for the Global Seasonality Score (GSS) of the French adaptation of the Seasonal Pattern Assessment Questionnaire (SPAQ), which assess seasonal change in mood, sleep duration, appetite, social activity, weight and energy level; 22 on the 29-item Structured Clinical Interview Guide for the Ham-D, SAD version (SIGH-SAD) with a score of 8 or more for the 8-item atypical symptoms in order to assess both the severity of depression and the presence of atypical symptoms. Assessment was performed by a clinical psychologist in training.

2.1.2. Healthy control group

None of the subjects classified as SAD according to a BDI-II score of $\leq$8, SIGH-SAD score of $\leq$11 and SPAQ global seasonal score (GSS) of $\leq$9. None of the subjects classified as S-SAD, which is a milder form of SAD in whom subjects show significant mood variations across seasons as demonstrated by a GSS of >9 but less than 11. According to the subject, symptoms must represent only a mild or moderate problem (Kasper et al., 1989; Kasper et al., 1989).

2.2. Protocol

All participants were exposed randomly to two light conditions for 60 min (red or blue) on two different days in winter time. To better control exposure, the light condition was delivered by a sphere called a Ganzfeld (Espion Color dome, Diagnosys LLC, Littleton, MA) that allowed a full field stimulation. Blue (420–520 nm; peak$\approx$470 nm;) exposure was set at 450 μW/cm^2 and red (600–670 nm; peak$\approx$635 nm) at 850 μW/cm^2. Based on measurements performed with a spectrometer (OceanOptics, Dunedin, FL), these intensities are equivalent to those found in the light therapy device at 10,000 lx (SADelite lamp, Northern Light, Montreal, QC, Canada) used in our previous study(Gagné et al., 2007). To avoid any risk of blue light hazard, a safety assessment was performed by an engineer and revealed that our blue light exposure was over 100 times below the toxicity threshold standard (ACGIH, 2007). It should be kept in mind, however, that this calculation is based on a single administration. On their way to the laboratory, all participants were instructed to wear dark sunglasses to reduce natural sunlight exposure that could interfere with the laboratory controlled light conditions. Light exposure always occurred between 9 h and 15 h.

2.3. Electroretinogram recordings

Similarly to Gagné et al. (2007), after each exposure, a full-field cone and rod ERG was performed in non-dilated eyes with DTL electrodes (Shieldex 33/9 Thread, Statex, Bremen, Germany) deeply secured into the conjunctival sac. Ground and reference electrodes (Grass gold cup electrodes filled with Grass EC2 electrode cream) were pasted on the forehead and external canthi (Hebert et al., 1995).

For the photopic ERG, participants were light adapted for 10 min to a white background light set at 80 cd s/m^2 provided by the same Ganzfeld device used for the experimental light conditions. A cone luminance-response function (LRF) was achieved using 13 white flash intensities ranging from 0.42 to 800 cd s/m^2. For the scotopic rod ERG, participants were first dark-adapted for 30 min before being stimulated with 12 green (peak: 509 nm) flash intensities ranging from 0.001 to 1 cd s/m^2 provided by the Ganzfeld in order to generate a rod luminance-response function (LRF).

2.4. ERG analysis

A two-way analysis of variance (ANOVA) with repeated measures for conditions was used to assess the effect of conditions and groups on the ERG Vmax, a-wave amplitude and Log K. The photopic Vmax