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Bright ambient light conditions reduce the effect of tryptophan depletion in healthy females

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ABSTRACT

Introduction: Tryptophan depletion (TD) is an established method to influence the serotonergic system and mood. The purpose of this study was to examine the effect of TD under different ambient light conditions, measured through serotonin-associated plasma levels and a visual analog scale (VAS), on healthy females.

Methods: Thirty-eight healthy female s-allele carriers of the serotonin transporter promoter gene (5-HTTLPR) were administered a TD under dim light conditions (75 lx). A sub-group of 8 participants repeated the procedure randomized in two additional light conditions (585 lx and 1530 lx respectively). Prior to, and 5 h following administration of TD, various variables (serotonin-associated plasma levels, VAS) were measured. Due to not normal distributed data, non-parametric statistical tests were used.

Results: Overall analysis showed a significant mood lowering effect of TD. Moreover, TD decreased all measured serotonin-associated plasma levels significantly. Significant differences in varying light conditions were found for the VAS and plasma tryptophan, with the greatest effect of TD in the 75 lx condition.

Conclusion: Results of our study showed an influence of even slight differences in ambient light intensity on the effect of TD concerning mood as well as on the serotonergic system.

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1. Introduction

Light is the most powerful synchronizer of the human biological clock located in the hypothalamic suprachiasmatic nucleus (SCN) (Hastings et al., 2008; Boivin et al., 1996). The SCN receives its non-visual inputs through the retinothalamic tract (RTT) from melanopsin-expressing retina ganglion cells which convert the signal of light into electrical signals (Hankins et al., 2008; Do and Yau, 2010). These signals are transmitted further to paraventricular nucleus, nuclei of the spinal cord, and finally to the pineal gland (Borjigin et al., 2011). The pineal gland contains the highest amount of the neurotransmitter 5-hydroxytryptamin (5-HT, serotonin). On a neurobiological level the production of serotonin is suggested to be directly related to bright light exposure through direct stimulation of the SCN (Brzezinski, 1997).

It is suggested that light-mediated effects are heterogeneous and dependent on light duration, light intensity and time of application (Borjigin et al., 2011). However, there is little knowledge regarding the dose–effect relation between light intensity and effects on neurobiological functions (Shirani and Louis, 2009). The use of bright light has been shown to have positive effects on depressive symptoms in the treatment of depression (Pail et al., 2011), as well as on vitality and distress in healthy individuals (Kasper et al., 1989; Partonen and Lonnqvist, 2000). While levels of normal indoor light range between 100 lx and 500 lx (~180 lx) (Zeitzer et al., 2000; Boivin et al., 1996), daylight provides around 800 lx in the morning and can reach up to 100,000 lx during the day. Most commonly used light therapy boxes offer between 2500 lx and 10,000 lx. Another, although less investigated model of light therapy is the treatment with ambient bright light settings. Ambient light settings with illumination levels between 300 lx and 2500 lx could offer economical, as well as practical means to combine therapeutic light application with daily activities in depressive patients.

Tryptophan depletion (TD) is a well-established method to reduce central nervous system (CNS) serotonin levels by depleting its precursor tryptophan through administration of a tryptophan-free mixture containing large neutral amino acids (LNAAs) as a competitor. Prior studies have demonstrated that the synthesis of central serotonin depends on the availability of tryptophan in the blood circulation of the brain (Nishizawa et al., 1997). The amount of

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tryptophan in the brain depends on its serum level and the concentration of several LNAAs such as valine, leucine, isoleucine, phenylalanine, and tyrosine (Fernstrom, 1983) in the bloodstream. LNAAs compete with tryptophan for the transport across the blood–brain barrier (Fernstrom and Wurtman, 1971). TD leads to a profound decrease of tryptophan levels in plasma and cerebrospinal fluid (CSF), effecting decreases in the levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in both bloodstream and CSF (Carpenter et al., 1998; Salomon et al., 2003; Williams et al., 1999). The administration of TD was used in a number of studies investigating the effect of transiently reduced serotonin transmission on mood (Lenzinger et al.,. 1999; Smith et al., 1997). Ellenbogen et al. (1996) demonstrated a significant lowering of mood in women but not in men after TD compared to the administration of sham depletion. Apart from female gender and a positive family history of depressive disorder, the genotype of the 5-HTTLPR polymorphism can influence the effect of TD (Neumeister et al., 2002; Walderhaug et al., 2007).

A pronounced effect of light exposure after TD was also observed in females suffering from seasonal changes of mood and behavior not sufficiently severe to meet the criteria of seasonal affective disorder (aan het Rot et al., 2008).

Concerning the effect of light on the serotonergic system, TD is able to reverse the effect of bright light (Lam et al., 1996) which stimulates serotonin synthesis. Vice versa the application of ambient bright light prevents the serotonin and mood reducing effect of TD (aan het Rot et al., 2008). This study addresses the question whether TD-induced changes in serotonergic metabolism, as well as self-rated mood, can be differently influenced by varying ambient light conditions. We used TD in a controlled study including female participants carrying one or two copies of the s-allele of the 5-HTTLPR gene. Based on previous studies (Walderhaug et al., 2007) which reported an enhanced effect of TD on women carrying one or two copies of the s-allele of the 5-HTTLPR gene compared to men, only female carriers with this genotype were recruited. We hypothesized that the established effect of TD, namely a worsening of mood paralleled by a decrease of plasma 5-HIAA, tryptophan and Tr/LNAA ratio, can be modulated by different ambient light conditions in healthy females. We suggest that ambient light with a brightness level even lower than that of common light therapy (2500 lx–10,000 lx) can significantly influence the effect of TD in a genetically vulnerable group.

2. Methods

This study was part of a larger project on the association of ambient light, mood, cognition and genetics (Defrancesco et al., 2011). To test our hypothesis we designed a trial in two steps one year apart (uncontrolled setting, 75 lx, randomized setting 585 lx followed by 1530 lx or vice versa).

2.1. Subjects

Two hundred and fifteen female undergraduate students were recruited at Innsbruck Medical University and Leopold-Franzens University Innsbruck in 2007/2008. These students completed a screening questionnaire regarding demographic data and general information about participants (age, education). All participants were screened for present or past Axis I diagnosis using the semi-structured clinical interview based on DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) and completed the following questionnaires: the NEO FFI, the Barrat Impulsivity Scale, the Hamilton Depression Rating Scale, and the Beck Depression Inventory. A smear test was taken via swaps to genotype all participants for 5-HTTLPR polymorphism. Following exclusion of ineligible probands, the remaining 38 female participants were invited to the first step of the study. Eleven participants were classified as s/s carriers and 27 as s/l carriers. Aside from being carriers of one or two copies of the s-allele, inclusion criteria included the absence of psychiatric or physical illness, as well as psychotropic medication. All participants had euthymic depression scores in the Beck Depression Inventory and the Hamilton Depression Rating Scale and had no history of Axis I diagnoses at baseline testing. All participants underwent a urine pregnancy test at the beginning of each test day. All 215 subjects were informed about the study design, which was approved by the Ethics Committee of Innsbruck Medical University, Austria, and gave written informed consent prior to participation in the study.

2.2. General study procedure

The study consisted of two consecutive steps. In step 1 all eligible subjects ($n=38$) completed the assessment under condition A (75 lx). In step 2 a sub-group of eight participants from the sample repeated the procedure randomized to 585 lx followed by 1530 lx or vice versa at the same time of year one year later.

Assessments of steps 1 and 2 were conducted in the month December, January and February of the years 2008/2009 and 2009/2010 to ensure that all participants arrive at the clinic for the test sessions before sunrise. Before inclusion in step 2 of the study the eight participants were reassessed using the same instruments mentioned above. Participants were invited by phone to participate in the study. They were instructed to refrain from drinking alcohol and caffeinated beverages and from eating any food on the three experimental mornings; only water or tea without sugar was permitted. The same restrictions were applied during the entire study day. Participants arrived in the hospital at 8.00 A.M. of each test day (duration of about 5 h). Accordingly blood samples were taken to analyze plasma levels of tryptophan, Tr/LNAA ratio, and 5-HIAA and participants completed a Visual Analog Scale (VAS) in which the current mood state was assessed twice (at baseline between 8.05 and 8.15 A.M. and 5 h after TD administration). To answer the VAS, participants were asked to rate their current mood on a scale ranging from -100 to $+100$. A score of $+100$ was defined as having extremely good subjective mood, a score of -100 was defined as having very bad subjective mood, and 0 was defined as neurtal mood mood. Following completion of baseline assessment, TD was administered. Participants were instructed to drink the amino acid mixture within 10 min. They stayed in a secluded room with constant room temperature in one of the three ambient light conditions for the duration of the procedure. This room had no other source of light. Participants were not informed about the actual light condition applied. Five hours after TD administration (between 1.20 and 1.30 P.M.) blood sampling and mood assessment were repeated. At the end of each test day participants received a snack rich in proteins and carbohydrates.

2.3. Description of standardized light conditions

For the documentation of standardized light conditions we measured ocular luminance levels with a standard luxmeter (Pocketlux; Fa. LMT Lichtmesstechnik, Berlin), light density with a fisheye objective (Canon EOS 350 D, Fa. TechnoTeam, Illmenau) and light spectrum with a spectroradiometer (Spectroradiometer specbos 1201, Fa. JETI Technische Instrumente GmbH, Jena). Further, UV radiation was filtered out. Table 1 presents details of the three standardized ambient light conditions.

2.4. Tryptophan depletion

TD was applied after completion of the baseline testing. The liquid contained 47.8 g of tryptophan free protein powder in a standard mixture of long neutral amino acids (LNAAs). The mixture consisted of 8 g L-isoleucin, 13.5 g L-leucin, 4.8 g L-lysin, 3 g L-methionine, 6.6 g L-phenylalanine, 3 g L-threonine and 8.9 g L-valine. 100 ml tap water and 100 ml sugar-free sirup were added to ease consumption.

2.5. Biochemical measurements

Blood samples were collected in 10 ml EDTA tubes and immediately centrifuged at 3000 rpm for 10 min at 4 °C. The plasma was then stored at -70 °C for analyses. Total plasma tryptophan levels, 5-HIAA and LNAAs, which were ingredients of the TD, were determined using high-performance liquid chromatography (HPLC) with fluorometric detection. All analyses were performed as described by Bongiovanni et al. (2001). The genotyping procedure for the identification of the s-allele carriers is described in detail elsewhere (Defrancesco et al., 2011).

Table 1
Detailed description of applied light conditions.

Light conditions	Luminous intensity Candela, cd (cd/m^2)	T (lx)	Color temperature Kelvin (K)
Condition A	33	75	3493
Condition B	274	585	6429
Condition C	770	1530	6298

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