



Correspondence

Humoral phototransduction: Light transportation in the blood, and possible biological effects

Summary In our measurements plasma and, especially, the main plasma protein, albumin, exhibits a long-lasting light-induced luminescence, which should be capable of transporting light along the blood circulation. Moreover, albumin shows intense fluorescence, with emission at 337 nm, which is controlled by bilirubin. Furthermore, it is known that tryptophan decarboxylase, the last step of serotonin formation, is directly activated by light, with a maximum at 337 nm.

As a hypothesis, we propose that light-induced luminescence of plasma components, such as albumin and free radicals, transports ambient light along the blood vessels. This emission could have photochemical and photobiological effects, e.g., photomodulation of enzymes. Albumin fluorescence emission could stimulate serotonin formation at 337 nm, modulated by bilirubin. Such mechanisms could be involved in the action of light therapy on serotonin formation, melatonin suppression and circadian rhythms, both in the pathophysiology of seasonal affective disorder and major depression, and in blood pressure regulation via photovasorelaxation. The proposed model can be called humoral phototransduction.

© 2008 Elsevier Ltd. All rights reserved.

Introduction

The action of light on serotonin conversion and circadian rhythms has been intensely studied for many years. So far, it seems clear that the effect is mediated by the eyes but not primarily through stimulation of the rods and cones. Two alternative mechanisms are under discussion. The first is a retinal photoreceptor, presumably melanopsin, which affects the suprachiasmatic nucleus (SCN) via the retinohypothalamic tract to reset the biological clock. A retinal photoreceptor, however, does not explain melatonin suppression and synchronized 24 h day and night cycles achieved by illuminating the back of the knees [1]. This phenomenon was called extraocular phototransmission, but could not be reproduced. As an alternative or complementary explanation, Oren published the humoral phototransduction hypothesis, postulating that bil-

irubin may act as a signal of light along the blood circulation [2]. This could act upon the eye because of the special optical properties and the good vascularisation of the retina. Countercurrent substance exchange in the cavernous sinus could allow direct access of the substance to the brain [3].

With these findings in mind, we started in vitro experiments with a very sensitive Hamamatsu-photomultiplier-tube (PMT) to find out what happens when whole blood is illuminated for a minute and put into the PMT. We found that whole blood after illumination does not reemit any light. In contrast, the same procedure with serum gives intense reemission for more than 10 minutes (see Fig. 1). By searching for plasma components responsible for the emission, we found that human serum albumin, the main plasma protein, gave an intense photonreemission for more than 25 min (see

Fig. 2). Literature on this phenomenon exists, but is mainly in Russian and not easily accessible in translation [4,5]. It is referred to by a variety of names, including ultraweak photonreemission, photoluminescence, induced chemiluminescence, and phosphorescence. Free radicals contribute to this emission.

Apart from light-induced luminescence, albumin shows fluorescence and two-photon excitation. Visible light is collected by the 585 amino acid molecule and transferred to a single tryptophan residue in position 214, where it is emitted at around 337 nm in the near UV region. This emission is quenched (reduced) by various substances, e.g., free fatty acids and bilirubin.

The bile pigment bilirubin was one of the two main candidates for the signal of light in Oren's humoral phototransduction hypothesis. It resembles phytochromes, which set the biological clock in plants. Its levels are reduced in seasonal affective disorder (SAD) patients [6]. It is bound to albumin with two binding sites that are 2.4 nm to the right and left of the single tryptophan residue [7]. Binding of bilirubin to albumin quenches the 337 nm emission. In this way, bilirubin controls the emission of fluorescence. The action spectrum of melatonin suppression has an optimum around 464 nm [8], matching the fluorescence excitation maximum of bilirubin of 462 ± 3 nm [9], and the most effective wavelength for conversion of bilirubin into photoproducts [10]. In 1989, Fraikin et al. showed that tryptophan decarboxylase, the second enzyme for serotonin formation, is activated by light at 337 nm [11]. Illumination of norepinephrine precontracted aortic rings of rabbits with a low-

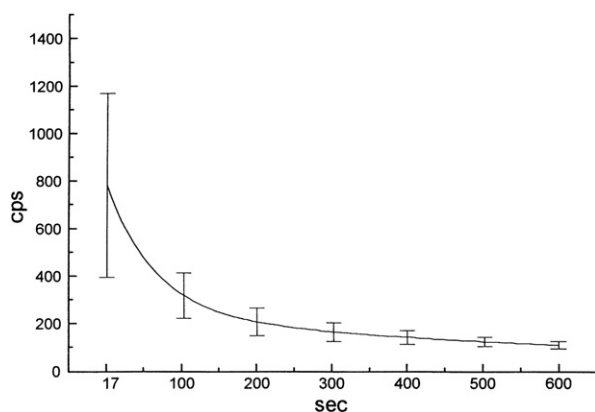


Figure 1 Light-induced luminescence of 5 ml plasma of three healthy volunteers. The plasma was illuminated for 1 min with a mercury gas lamp. Photon emission was recorded in a Hamamatsu photomultiplier. Measurement started 17 s after the illumination, cps = counts per second = emission.

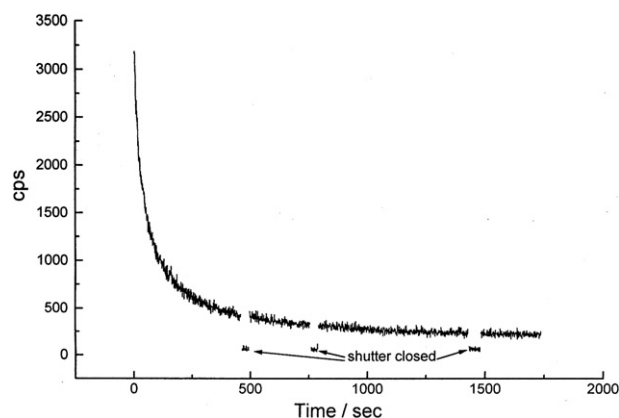


Figure 2 Light-induced luminescence of 5 ml human serum albumin 30 g/100 ml at pH 7.4. The specimen was illuminated for 30 s. Measurement started 32 s after the illumination. Note that the emission is high despite a shorter illumination time and longer transfer time. Twenty-five minutes after the illumination, the emission is still higher than the background (shutter closed), cps = counts per second = emission.

power laser causes a relaxation of the rings. The maximum of this effect occurs, again, near 337 nm [12]. It has been termed photovaso-relaxation. All in all, it seems that the spectral region of the tryptophan fluorescence emission is of special biological interest.

The hypothesis

Light reaches the blood vessels of the retina easily, but also penetrates the skin. In the capillaries where plasma and erythrocytes are separated, plasma components such as albumin and free radicals should be activated to luminescence, which can be expected to transport light along the blood vessels. With a circulation time of <10 s, this emission should be relatively high. Light generated within the body by metabolic reactions, also called biophotons, could contribute to this luminescence. A broad spectrum of photochemical and photobiological effects could be influenced by this emission, such as photomodulation of enzymes or photovaso-relaxation. This light would also generate fluorescence emissions at 337 nm and other wavelengths. It could directly stimulate tryptophan decarboxylase and, thus, serotonin formation. Also, melatonin suppression and blood pressure could be affected. The proposed mechanism of light transportation along the circulation can be called humoral phototransduction, since humor is Greek for liquid, and includes blood.

Evaluation of this model and possible experiments

Questions arise from the possible activation of tryptophan decarboxylase which, according to some authors, is not the rate-limiting enzyme in serotonin formation. Furthermore, Fraikin et al. have performed their experiments with yeast, so it remains to be shown that tryptophan decarboxylase is identical to L-aromatic-aminoacid-decarboxylase (AADC) in humans, and that AADC is also light activatable in the 337 nm spectral region. Indeed, AADC is light activatable (at least in the retina of the rat) [13].

A 337 nm low-power laser relaxes norepinephrine precontracted aortic rings of rabbits. If tryptophan emission produces similar effects that take place in the capillaries, where plasma and erythrocytes are separated, this should influence the blood pressure. And indeed, infusions of albumin produce a marked hypotension [14]. On the other hand, loss of albumin during plasmapheresis results in increased short-term variability of both the systolic and diastolic pressure [15]. The hypothesis also fits for pregnancy, where low albumin is correlated with hypertension [16], but not for end stages of renal disease and hemodialysis, where low albumin is associated with hypotension [17]. Concerning tryptophan decarboxylase, it has been reported that albumin is lower in individuals with major depression [18], in the first episode of schizophrenia [19] and in panic disorder, which are all associated with lower serotonin levels. Bilirubin could have a special role in this system: it is bound to albumin, it quenches the near 337 nm emission, it is readily converted into photoproducts and, together with biliverdin, it binds to the aryl hydrocarbon receptor [20] that influences serotonin levels and circadian rhythms. Also, other substances quenching the 337 nm emission of albumin could have an effect, e.g., free fatty acids, and, indeed, infusions of free fatty acids raise the blood pressure [21]. However, the proposed model does not fit for infusions of bilirubin, which quench the tryptophan emission; they actually tend to lower the blood pressure. The transportation of light along the blood circulation could be shown by placing the foot of a volunteer in a dark room and recording the light emission from the skin of the forefoot with a photomultiplier. The application of light therapy to the eye would increase the light emission from the foot, and an interruption of the blood circulation with a pressure cuff should prevent that increase.

Discussion

Small quantities of light have been shown to be involved in cell to cell communication. Van Wijk has summarized these experiments and their history in detail [22], so the idea that light regulates reactions inside the body is not new. Our ideas on this subject were presented in Medical Hypotheses earlier [23]. As stated before, it is very likely that light is transported along the blood vessels by albumin, other plasma components, free radicals and white blood cells. The question is, how much light is involved and whether it is strong enough to have biological effects. The idea that neurotransmitter formation and release could be influenced by low levels of light is not new. In fact, such an effect has been shown for γ -amino butyric acid [24]. Moreover, it has been shown that the putative photoreceptor encephalopsin is expressed in various areas of the cerebral cortex, in cerebellar Purkinje cells and, to a much lesser degree, even in liver and spleen tissue [25], in areas where ambient light can hardly be expected.

Humoral phototransduction could be responsible for a broad spectrum of effects. More experiments could help to calculate the magnitude of the emission and to clarify possible effects. Everything, from no effect at all to a major role for the mechanisms proposed, is possible. Light transportation by the blood and mood control by bile pigments calls to mind the ancient Greek theory of humorism, with the idea that the balance of "humors" influences the physical health.

References

- [1] Campbell SS, Murphy PJ. Extraocular circadian phototransduction in humans. *Science* 1998;279(5349):396–9.
- [2] Oren DA. Humoral phototransduction: blood is a messenger. *Neuroscientist* 1996;2:207–10.
- [3] Grzegorzewski WJ, Skipor J, Wasowska B, Krzymowski T. Countercurrent transfer of 125I-LHRH in the perihypophyseal cavernous sinus-carotid rete vascular complex, demonstrated on isolated pig heads perfused with autologous blood. *Domest Anim Endocrinol* 1997;14(3):149–60.
- [4] Zhuravlev AI, Asonov MA. Sensitivity and functional characteristics of modern chemoluminescence meters. *Biofizika* 1991;36(3):489–98. Russian.
- [5] Sapezhinski II, Dontsova EG, Shiriaev VM. Photooxidation and photochemiluminescence of different proteins. *Biofizika* 1979;24(3):386–91. Russian.
- [6] Oren DA, Desan PH, Boutros N, Anand A, Charney DS. Effects of light on low nocturnal bilirubin in winter depression: a preliminary report. *Biol Psychiatry* 2002;51(5): 422–5.
- [7] Honoré B, Pedersen AO. Conformational changes in human serum albumin studied by fluorescence and absorption spectroscopy. Distance measurements as a function of pH

- and fatty acids. *Biochem J* 1989;258(1):199–204.
- [8] Brainard GC, Hanifin JP, Greeson JM, Byrne B, Glickman E, Gerner E, et al. Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *J Neurosci* 2001;21(16):6405–12.
- [9] Glushko V, Thaler M, Ros M. The fluorescence of bilirubin upon interaction with human erythrocyte ghosts. *Biochim Biophys Acta* 1982;719(1):65–73.
- [10] Isoke K, Itoh S, Onishi S, Yamakawa T, Ogino T, Yokoyama T. Kinetic study of photochemical and thermal conversion of bilirubin IX alpha and its photoproducts. *Biochem J* 1983;209(3):695–700.
- [11] Fraikin GY, Strakhovskaya MG, Ivanova EV, Rubin AB. Near-UV activation of enzymatic conversion of 5-hydroxytryptophan to serotonin. *Photochem Photobiol* 1989;49(4):475–7.
- [12] Chaudhry H, Lynch M, Schomacker K, Birngruber R, Gregory I, Kochevar I. Relaxation of vascular smooth muscle induced by low-power laser radiation. *Photochem Photobiol* 1993;58(5):661–9.
- [13] Hadjiconstantinou M, Rossetti Z, Silvia C, Krajnc D, Neff NH. Aromatic L-amino acid decarboxylase activity of the rat retina is modulated in vivo by environmental light. *J Neurochem* 1988;51(5):1560–4.
- [14] Howard G, Downward G, Bowie D. Human serum albumin induced hypotension in the postoperative phase of cardiac surgery. *Anaesth Intensive Care* 2001;29(6):591–4.
- [15] Girard A, Phan ML, Weise F, Elghozi JL. Effects of plasmapheresis on short-term variability of blood pressure in healthy donors. *Clin Auton Res* 1992;2(5):299–302.
- [16] Brown MA, Buddle ML. Hypertension in pregnancy: maternal and fetal outcomes according to laboratory and clinical features. *Med J Aust* 1996;165(7):360–5.
- [17] Iseki K, Miyasato F, Tokuyama K, et al. Low diastolic blood pressure, hypoalbuminemia, and risk of death in a cohort of chronic hemodialysis patients. *Kidney Int* 1997;51(4):1212–7.
- [18] Huang SY, Chiu CC, Shen WW, Chang HC, Wu PL, Su KP. Hypoalbuminemia in drug-free patients with major depressive disorder compared with a dietary matched control group: a clinical meaning beyond malnutrition. *Eur Neuropsychopharmacol* 2005;15(2):227–30.
- [19] Reddy R, Keshavan M, Yao JK. Reduced plasma antioxidants in first-episode patients with schizophrenia. *Schizophr Res* 2003;62(3):205–12.
- [20] Phelan D, Winter GM, Rogers WJ, Lam JC, Denison MS. Activation of the Ah receptor signal transduction pathway by bilirubin and biliverdin. *Arch Biochem Biophys* 1998;357(1):155–63.
- [21] Monahan KD, Dyckman DJ, Ray CA. Effect of acute hyperlipidemia on autonomic and cardiovascular control in humans. *J Appl Physiol* 2007;103(1):162–9. Epub 2007.
- [22] Van Wijk R. Bio-photons and bio-communication. *J Sci Explor* 2001;15(2):183–97.
- [23] Grass F, Klima H, Kasper S. Biophotons, microtubules and CNS, is our brain a “holographic computer”? *Med Hypotheses* 2004;62(2):169–72.
- [24] Wade PD, Taylor J, Siekevitz P. Mammalian cerebral cortical tissue responds to low-intensity visible light. *Proc Natl Acad Sci USA* 1988;85(23):9322–6.
- [25] Blackshaw S, Snyder SH. Encephalopsin: a novel mammalian extraretinal opsin discretely localized in the brain. *J Neurosci* 1999;19(10):3681–90.

F. Grass

S. Kasper

Department for Biological Psychiatry

Medical University of Vienna

1090 Waehringer Guertel 18-20

Vienna, Austria

Tel./fax: +43 6643585175

E-mail address: friedrich.grass@chello.at (F. Grass)

Available online at www.sciencedirect.com

