Medical Hypotheses 129 (2019) 109248

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

A new theory based on possible existence of timing control by intracellular photons in tonically active neurons

Hossein Mofidi, Yashar Sarbaz*, Saeed Golmohammadi

School of Engineering Emerging Technologies, University of Tabriz, Tabriz, Iran

ARTICLE INFO

Keywords:
Time perception
Tonically active neuron
Photoreceptor
Timing mechanism
Oscillating rhythm

ABSTRACT

Time perception in living organisms, especially mammals, and understanding the timing of their internal organs, have always been the topic of interest in neuroscience. In this study, our theory considers the photonic behavior on time control by some particular or some block of neurons. Photon emission by mitochondria has regular timing in intercellular process. In other words, due to the main mitochondrial function of cellular respiration as well as the source of photon emission, it is possible to deduce photon at a specific rate in TANs (Tonically Active Neurons). If photoreceptors exist in the neurons of the nervous system, photons can be received at a regulated time. Thereby, neurons can produce a constant-frequency signal for subsequent stimuli. Our studies conducted in the CNS (Central Nervous System) and TANs, and it seems that photoreceptors are present in TANs. Photons are interpreted by a series of neurons and produce an oscillating rhythm. These rhythms can be the basis of the body's chronological activity in different areas of the CNS. If this hypothesis is true, it can be deduced that an independent factor, excluding circadian activities, exists for living activities. Different neuronal structures will also be responsible for understanding the time. Although this hypothesis is far from a complete evaluation, it can compensate for some of the other problems. For instance, a series of inconsistencies that occur in some neurological diseases, such as Parkinson diseases can be well justified by this hypothesis.

Introduction

Thinking about time has been one of the most important concerns of mankind. From a long time ago, the perception and the way of feeling of time have been the center of attention. Despite all studies in the past decades to perceive the time mammals internal organs, this issue has not been completely deciphered. Time perception has been investigated through different branches of science, such as philosophy, astronomy, mathematics, neurosciences. Description of how creatures, especially humans, perceive the time is one of the most important concerns activities of the time perception. Much attention is also given to how mammals feel and perceive the time by their internal organs which leads to adjusting the trend of their activities. Various theories have been presented in this case which the theory of circadian rhythms and biological clock are the most notable ones [1–4].

Researchers have done a great deal of research about perception and identification of the biological clock and synchronization among body's organs during their activities [4–12]. According to research, conducted by P. Nongkynrih and V. K. Sharma in 1992, light and temperature are the most prevalent factors among all factors that affect the biological rhythms. In this way, light changes in day and night can activate or deactivate genes that control the molecular structure of biological clocks. In other words, changing the period of day and night as well as the circadian rhythm can slow down, speed up or even reset the biological clock [4]. Based on the research of G. C. Brainard and J. P. Hanifin in 2005, light affects the human consciousness deeply through the stimulation of the nervous system, which has widespread effects on almost all tissues in the body in turn. However, the interaction between clocks in central nerve tissues and peripheral nerve tissues has not been fully understood and has remained as a challenge [10]. The analysis of R. Laje et al. in 2011 shows that the occurrence of successive events in the body does not depend on resetting an internal timer in each event, and it seems that it is in the framework of a general pattern [13]. The aims of Urs Albrecht in 2012, to examine the relationship between biological clock, metabolism, the impacts of light and food on the circadian system, indicated that the circadian system directly affects the disorders, including metabolic and mood disorders [7]. In 2016, N. F. Hardy and D. V. Buonomano argued that the brain has a number of different timing mechanisms, and each of them is used to solve a certain time tasks [14]. In 2018, S. Hood and S. Amir argued that there are predictable rhythms in the expression of anger, the natural rhythm of physiological, aggressive activities affect and intensify each other

* Corresponding author at: Department of Mechatronics Engineering, School of Engineering Emerging Technologies, University of Tabriz, Tabriz, Iran.
E-mail address: yashar.sarbaz@tabrizu.ac.ir (Y. Sarbaz).

https://doi.org/10.1016/j.mehy.2019.109248
Received 6 March 2019; Received in revised form 19 May 2019; Accepted 24 May 2019

mutually. Daily system dysfunction can increase the probability of aggressive behaviors and conversely, chronic expression of anger can disturb the natural rhythm of physiological activity and create conditions for diseases, such as cardiovascular disease [15]. Y. Sarbaz, H. Pourakbaria in 2019 investigated the basal ganglia function in people with Parkinson's disease. They found the evidence of the existence of some asynchronicity between motor tasks and cognitive behavior [16].

In the past decades, researchers have made considerable progress about biological clock, brain, body rhythms and factors such as genes and circadian light that are received by eyes. These are expressed as the provocative and influential factors that influencing the clock and body rhythms. However, these ideas cannot be considered as a complete and independent list of factors to justify the basic structure of rhythms and body functions. Indeed, the body perform its' main activities independently and regardless of its position on the ground or even day and night; such as the digestive system, the nervous system, and the motor system. Therefore, it is necessary to seek an internal source of time in the body which is dependent on a regular and reliable mechanism that contains the time production concept. But it seems that there is no comprehensive, stable, and reliable theory about the nature and function of the body rhythm and biologic clock yet. This study tries to provide an acceptable hypothesis based on the behavior of observed photons in the neurons.

Hypothesis

In general, the main source of time perception can be considered in the form of nervous system processing. This study will be based on the theory of time control and time perception by specific neurons (Tonically active neurons). Tonically active neurons have been seen in the human body and these are active spontaneously. Furthermore, there is an intracellular photon emission in Tonically active neurons. In intracellular behaviors, photon emission in the mitochondria has a regular behavior and especial timing [17–19]. In addition, there are photoreceptors in some part of CNS and PNS (Peripheral Nervous System) [21]. According to studies about the CNS and tonically active neurons, it seems that photoreceptors are present in these tonically active neurons [20–24]. If these photoreceptors exist in the neurons of the nervous system, reception of photons is possible at a constant time, which consequently the neuron will produce a constant-frequency signal for subsequent stimulations. It can be concluded that the part of excitation and permanently oscillation of these neurons may be due to photon emission and their reception by photoreceptors in these neurons. As a result, these neurons can be a good standard for time because of their regular fluctuations. Based on this hypothesis, the root of the biological clock inside the body is the regular photon emission by mitochondria, which is interpreted by a number of neurons and generates an oscillating rhythm. These rhythms in different regions of the CNS can be the basis for controlling the time of the body's activities.

Evaluation

In Fig. 1, the main hypothesis relating to the process of producing a significant time basis by photon in tonically active neurons is shown in six steps as a diagram. The intended process is in this form that photons are produced by chemical processes within the mitochondria. These photons are absorbed by optical receptors which are present in some neurons, including Tonically active neurons. Optical receptors send a signal in their own neuron after photon absorption that triggers the neuron stimulation and the action potential sake of the photon. Then, the stimulated neuron contributes to stimulation of the neurons attached to this neuron and since all of this process is happening in constant frequencies generated from the photon produced in the mitochondria; it can be said that the oscillations of these neurons, which are the result of the intracellular emitted photon, are the basis for the timing of the body's organs.

The initial idea of this theory emanates from the presence of a photon in the neuron. In general form to emission a photon, electrons get stimulated by the energy that is given to them and they go to a higher energy level, they emit photons when they lose their own energy and return to lower energy level. An energy source for producing photons in mitochondria is an enzyme process called *oxidative phosphorylation* in which the ATP gets produced [17]. The chain of electron transfer in the mitochondria contains proteins that are located in three complexes of respiratory enzymes: 1. the NADH dehydrogenase complex, 2. the cytochrome complex, 3. the cytochrome oxidase complex. These respiratory complexes contain metal ions and chemical groups that provide a pathway for electron movement. The energy to pump the proton from the matrix to space between the two membranes, generated by the transfer of high-energy electrons which first create a proton concentration gradient across the mitochondrial membrane and then contribute to the membrane potential resulted from mitochondrial membrane's sides. The electrochemical steep gradient of protons and the proton getting back to the matrix is the result in sum of the concentration gradient and membrane potential. As can be seen, pumping up to a high level is done in Fig. 2.A and a downside change of level has occurred in Fig. 2.B. The pathway of the proton across the mitochondrial wall and following that the electron transfer from the donor to acceptor is shown in Fig. 3. When the lifespan of the electron energy in higher energy level comes to end, it gets transmitted to the lower energy level (from acceptor to donor) as shown in Fig. 2.B. This electron backward, from higher-energy levels to lower energy levels leads to release of energy called *photon*.

The main task of the neuron is to transmit information by electrochemical signals. Based on studies the photons cannot transmit signal and be a good complement to electrochemical signals because of emission rates per neuron seem to be quite low in comparison with electrochemical signals rates. On the other hand, it is concluded that these photons are produced by mitochondria at the rate of one photon per minute. The rate of photon emission refers to scattered photons. The rate of photon emission was used based on experiments in [25–28]. Maybe if the same experiments carried out in another part of the brain, This rate might be different. We do not insist that this rate is constant throughout the body. The range of wavelength in the whole body is from NUV (near UV) to NIR (near IR) and have a constant rate over time. note that the emission rates and its range could be very different depending on the neuron type [17,20,25–28]. Therefore, it can be assumed that the way of timing in body and emission of photons has a close relationship.

Eq. (1) calculates the energy of a photon emitted in mitochondria with electron-volt unit [17]:

$$\bar{V} = \frac{\Delta E_q N}{x^3}(-4800)cm^{-1} \quad (1)$$

where ΔE is the energy variation with units of $L(L+1) - 3L_z^2$ when the value of the rotational angular momentum component is $\pm$ 2, $\pm$ 1, or zero. As a result, the positive value of ΔE can be 9, 12 and 3. The q parameter represents the voltage of the carbon atoms, which can be between 2 and 4, and N is the total number of carbon atoms in the ring, which is estimated, its range can be from 30 to 36. Here X represents a multiple of a_0 that forms the radius of the circle, it means thata $= \mathrm{x}a_0$. X can be variable between $x = 10$ and $x = 20$. Therefore, the largest positive integer $\bar{V}$ will be equal to $1.04eV$.

Based on practical measurements, it can be said that the process and mechanism of photon emission in mitochondria can be cause of a particular energy and rhythm [17,18,20]. Since these produced photons cannot be conceptualized alone, therefore, there must be receptors for them. These photoreceptors have been found in brain sections such as plasma membrane of cell somas, dendrites, cerebellar, spines and terminals in the striatum and VL (Ventral lateral nucleus) [21,22]. Various studies show photon stimulation of neurons. In these studies, the neurons get stimulated by external light with desirable wavelengths

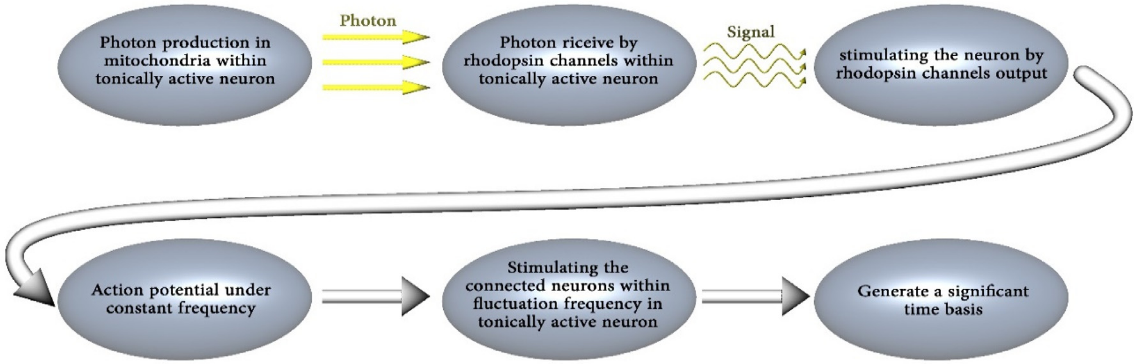

Fig. 1. The process of producing a significant time basis by intercellular photon within active tonically neurons.

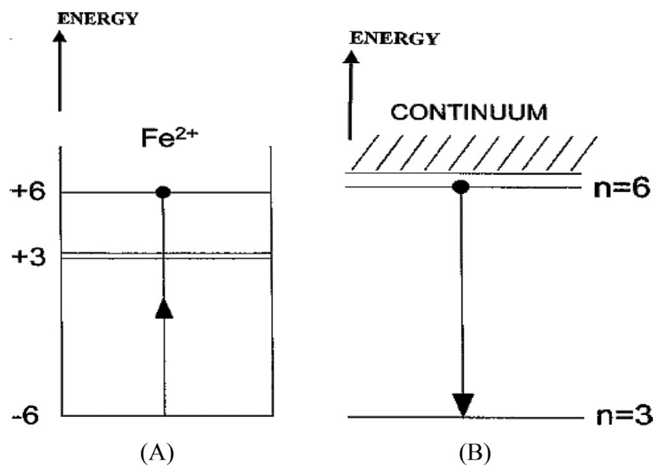

Fig. 2. Stimulation of an electron to a high energy level and then a downward change of energy level from n = 6 to n = 3 [17]. A: stimulation of Fe^{+2}, an electron to a proton. B: downward change of energy level from n = 6 to n = 3.

leading to the action potential reception of that neuron [29–34]. In Table 1, the optical characteristics of white and gray brain matters have been investigated. In these two parts of the brain, some factors such as absorption coefficient, scattering coefficient, anisotropic factor, reduced scattering coefficient and the depth of light penetration, respectively have been investigated in different wavelengths and compared with previous experiments [34].

Tonically active neurons have been found in some parts such as Retina, Basal ganglia, cerebellum. Among the studies conducted about the CNS and tonically active neurons and also, some studies have pointed to the presence of photoreceptors in these neurons [19,21,31]. If photons which are produced by mitochondria have enough energy and also have sufficient photoreceptors in certain neurons, can lead to the regular and permanent activity in those particular neurons. The rate of photon emission might be vary depending on a different part of the brain. On the other hand, we have evidence to explain that the time distribution in neural activity is related to each other as a network. Furthermore, TANs working as a network in pairs of other cells TANs [35]. So, the activation of one neuron may result in activation or inactivation other subsequent layers of neurons. For example, by activation of one neuron in every 1-minute, forward layers may fire every 7-minute. If we find the same process in our motor activity, there are different patterns could generate in other cells according to this simple clock (Central Pattern Generators' behavior). We're working on to describe it more. As we know, the effects of circadian rhythm on body activities are known. In this way, it can be said that the timing of body activities is primarily influenced by the internal factor and then other external factors such as circadian rhythm.

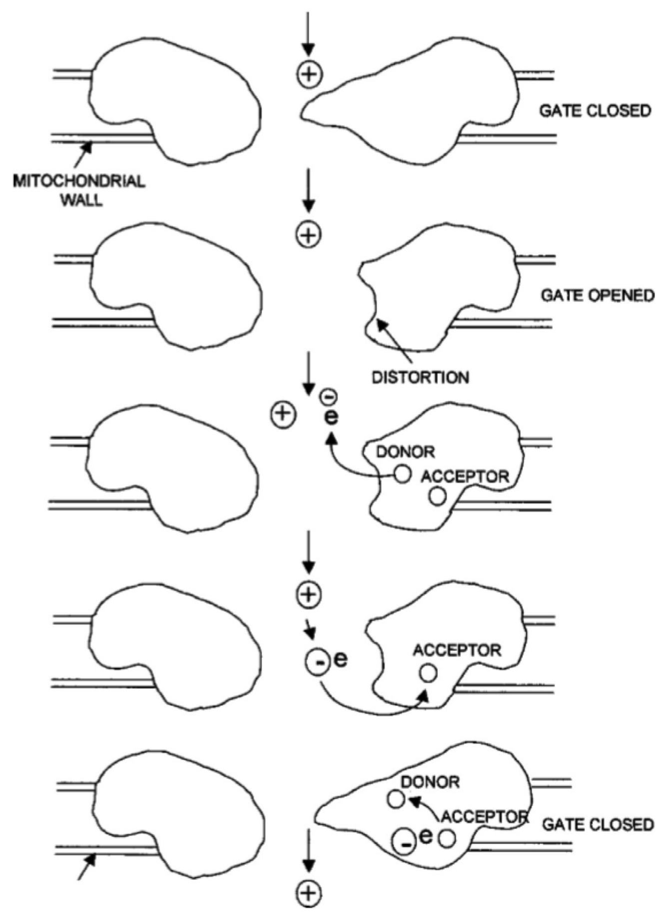

Fig. 3. Proton passes through a hole in the mitochondria wall that transmits the electron between donor and acceptor states. The proton, by distortion of the heme group, "Gets open", sends the electron freely to the receiver's site. Donors and acceptors return to their original state and the gates are closed [17].

Conclusion

In this study, a hypothesis is introduced to explain the photonic neuronal behaviors for the time perception in some creatures like a human. According to this hypothesis, the photon is generated with a distinct rhythm in the neurons, and this rate can be the basis for the neuronal time function. Although this hypothesis is not completely evaluated yet, it can compensate some of the problems in timing activities.

If we assume that the hypothesis based on time activities by photons is possible, It could be justify some inconsistency of time between motor

Table 1
Optical Characteristics of Human Brain Tissues and (*) is results of A N Yaroslavsky et al. in 2002 [34].

Biotissue	$\lambda(nm)$	$\mu_a(mm^{-1})$	$\mu_s(mm^{-1})$	g	$\mu'_s(mm^{-1})$	$\delta_{eff}(mm)$	References
White brain matter	456	0.81	92.3	0.92	7.384	0.22	Gottschalk (1992) [36]
	450	0.14	42.0	0.78	9.24	0.5	*
	514	0.5	104.5	0.93	7.315	0.29	Gottschalk (1992) [36]
	510	0.1	42.6	0.81	8.094	0.64	*
	630	0.15	38.6	0.86	5.404	0.63	Gottschalk (1992) [36]
	630	0.08	40.9	0.84	6.544	0.79	*
	675	0.07	43.6	0.87	5.668	0.83	Gottschalk (1992) [36]
	670	0.07	40.1	0.85	6.015	0.83	*
	850	0.08	14	0.95	0.7	2.3	Roggan et al (1994) [37]
	850	0.1	34.2	0.88	4.1	0.9	*
	1064	0.16	51.3	0.95	2.565	0.88	Gottschalk (1992) [36]
	1064	0.04	11	0.95	0.55	3.76	Roggan et al (1994) [37]
	1064	0.1	29.6	0.89	3.256	1.0	*
Grey brain matter	456	0.9	68.6	0.95	3.43	0.29	Gottschalk (1992) [36]
	450	0.07	11.7	0.88	1.404	1.84	*
	514	1.17	57.8	0.97	1.734	0.31	Gottschalk (1992) [36]
	510	0.04	10.6	0.88	1.272	2.52	*
	630	0.14	47.3	0.93	3.311	0.83	Gottschalk (1992) [36]
	630	0.02	9.0	0.89	0.99	4.06	*
	675	0.06	36.4	0.91	3.276	1.29	Gottschalk (1992) [36]
	670	0.02	8.4	0.9	0.84	4.4	*
	1064	0.19	26.7	0.96	1.07	1.18	Gottschalk (1992) [36]
	1064	0.05	5.7	0.9	0.57	3.28	*

tasks and cognitive tasks. For example, our previous study in Parkinson's disease has been shown that the time functionality of cognitive behavior and motor tasks are separated from each other. Our empirical study has been shown when Parkinsonian patients are asked to count their paces' number during walking in the middle and severe stages of the disease, they have a remarkable error in counting their paces' number [16]. It shows obviously the walking process that belongs to the damaged basal ganglia is different from the counting process that belongs to another part of the brain. This doesn't happen in healthy people. So, we can conclude that photon emission can be used as a reliable factor for perceiving time. But due to damaged some parts of central nervous system (Substantia Nigra Pars Compacta) and its effect on the Striatum), the regular process in perceiving the timing behavior of photons has been disturbed. Then perceiving time differs from the motor task and cognitive behavior.

To improve this theory, an independent source of circadian light activities can be considered for living activities. Moreover, since different neuronal structures will be responsible for time perception, the time inconsistencies in some neurological diseases, such as Parkinson's disease can be well explained by this hypothesis. At the end, the challenge of not understanding the interaction of biological clocks on neural tissues remains from G. C. Brainard and J. P. Hanifin studies in 2005, can be somehow explained [10]. Followingly, the experimental study of photonic neuronal behaviors are recommended in the mentioned fields. We hope the proposed hypothesis in this study would elucidate the riddle of synchronization and time control in the Striatum.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109248.

References

[1] Whitelam GC, Millar AJ. Light regulation and biological clocks. Ann Plant Rev 2018;1:349–78.
[2] Nongkynrih P, Sharma VK. Biological clocks: mechanisms and developments. J Photochem Photobiol B 1992;13(3–4):201–17.
[3] Light E, In P, Of E, Clock B. Light Regimen. 1967. p. 414–21.
[4] Feillet CA, Albrecht U, Challet E. 'Feeding time' for the brain: a matter of clocks. J Physiol Paris 2006;100(5–6):252–60.
[5] Gonfalone AA. Sleep and gravity. Med Hypotheses 2018;113:81–4.
[6] Ye F, et al. Proposed mechanisms of relative bradycardia. Med Hypotheses 2018;119:63–7.
[7] Albrecht U. Timing to perfection: the biology of central and peripheral circadian clocks. Neuron 2012;74(2):246–60.
[8] McClung CA. Circadian genes, rhythms and the biology of mood disorders. Pharmacol Ther 2007;114(2):222–32.
[9] Buonomano DV, Laje R. Population clocks: motor timing with neural dynamics. Trends Cogn Sci 2010;14(12):520–7.
[10] Brainard GC, Hanifin JP. Photons, clocks, and consciousness. J Biol Rhythms 2005;20(4):314–25.
[11] Sharma V. Role of sleep deprivation in the causation of postpartum obsessive-compulsive disorder. Med Hypotheses 2019;122:58–61. https://doi.org/10.1016/j.mehy.2018.10.016.
[12] Scherer CA, Miller SI. Molecular pathogenesis of salmonellae. Principles of Bacterial Pathogenesis Elsevier; 2001. p. 265–333. https://doi.org/10.1016/B978-012304220-0/50008-X.
[13] Laje R, Cheng K, Buonomano DV. Learning of temporal motor patterns: an analysis of continuous versus reset timing. Front Integr Neurosci 2011;5:1–11.
[14] Chanpimol S, et al. Neurocomputational models of interval and pattern timing. Curr Opin Behav Sci 2016;8(310):250–7.
[15] Hood S, Amir S. Biological clocks and rhythms of anger and aggression. Front Behav Neurosci 2018;12:1–12.
[16] Sarbaz Y, Pourakbari H. The effects of counting the stride numbers on the parkinsonian gait: suggesting a possible reason for dual task interference. Basic Clin Neurosci J 2019;10(3):269–79.
[17] Tuszyński JA, Dixon JM. Quantitative analysis of the frequency spectrum of the radiation emitted by cytochrome oxidase enzymes. Phys Rev E – Stat Phys Plasmas Fluids Relat Interdiscip Top 2001;64(5):7.
[18] Buzsáki G, Mizuseki K. The log-dynamic brain: how skewed distributions affect network operations. Nat Rev Neurosci 2014;15(4):264–78.
[19] Galvan A, Hu X, Smith Y, Wichmann T. In vivo optogenetic control of striatal and thalamic neurons in non-human primates. PLoS One 2012;7(11).
[20] Kumar S, Boone K, Tuszyński J, Barclay P, Simon C. Possible existence of optical communication channels in the brain. Sci Rep 2016;6:1–13.
[21] Tang R, Dai J. Spatiotemporal imaging of glutamate-induced biophotonic activities and transmission in neural circuits. PLoS One 2014;9(1):1–8.
[22] Schalken JJ, et al. Immunocytochemical evidence of molecular photoreceptor markers in cerebellar medulloblastomas. Cancer 2006;60(8):1763–6.
[23] Lenz JD, Lobo MK. Optogenetic insights into striatal function and behavior. Behav Brain Res 2013;255:44–54.
[24] Aosaki T, Tsubokawa H, Ishida A, Watanabe K, Graybiel AM, Kimura M. Responses of tonically active neurons in the primate's striatum undergo systematic changes during behavioral sensorimotor conditioning. J Neurosci 1994;14(6):3969–84.
[25] Kobayashi M, et al. In vivo imaging of spontaneous ultraweak photon emission from a rat's brain correlated with cerebral energy metabolism and oxidative stress. Neurosci Res 1999;34(2):103–13.
[26] Albrecht-Buehler G. Cellular infrared detector appears to be contained in the centrosome. Cell Motil Cytoskeleton 1994;27(3):262–71.

[27] Kataoka Y, et al. Activity-dependent neural tissue oxidation emits intrinsic ultra-weak photons. Biochem Biophys Res Commun 2001;285(4):1007–11.
[28] Wang Z, Wang N, Li Z, Xiao F, Dai J. Human high intelligence is involved in spectral redshift of biophotonic activities in the brain. Proc Natl Acad Sci 2016;113(31):8753–8.
[29] Kunduri G, et al. Defective cortex glia plasma membrane structure underlies light-induced epilepsy in *cpes* mutants. Proc Natl Acad Sci 2018;115(38):E8919–28.
[30] Brown J, et al. Expanding the optogenetics toolkit by topological inversion of rhodopsins. Cell 2018;175(4):1131–40.
[31] Kralj JM, Douglass AD, Hochbaum DR, MacLaurin D, Cohen AE. Optical recording of action potentials in mammalian neurons using a microbial rhodopsin. Nat Methods 2012;9(1):90–5.
[32] Batabyal S, et al. Label-free optical detection of action potential in mammalian neurons. Biomed Opt Express 2017;8(8):3700.
[33] Diester I, et al. An optogenetic toolbox designed for primates. Nat Neurosci 2011;14(3):387–97.
[34] Yaroslavsky A, et al. Optical properties of selected native and coagulated human brain tissues. Phys Med Biol 2002;47:2059–73.
[35] Raz A, et al. Neuronal synchronization of tonically active neurons in the striatum of normal and parkinsonian primates. J Neurophysiol 1996;76(3):2083–8.
[36] Gottschalk WK, et al. The carboxy terminal 110 amino acid portion of the insulin receptor is important for insulin signalling to pyruvate dehydrogenase. Biochem Bioph Res Co 1992;189(2):906–11.
[37] Roggan A, et al. Determination of optical tissue properties with double integrating sphere technique and Monte Carlo simulations. Proc SPIE 2100 1994(3):42–56.