NEURAL REGENERATION RESEARCH
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The code of light: do neurons generate light to communicate and repair?

Cecile Moro, Ann Liebert, Catherine Hamilton, Nicolas Pasqual, Glen Jeffery, Jonathan Stone, John Mitrofanis*

A great challenge in neuroscience has been to understand how neurons communicate. The neuroanatomists of the 19th Century could see neurons stretching processes to contact other neurons, but could not see the detail of the contact. Many thought that neurons formed a syncytium, with continuity of membranes from one to the next. Over the ensuing two hundred years or so, we have come to understand that the circuity of the brain is not formed by a syncytium of neurons; rather, individual neurons communicate with each other with a range of biological signals. Neurons are highly active cells, with their activity being electrical and their communication being either chemical, electrical or gaseous.

Although first proposed about a century ago, another form of communication between neurons has been attracting attention in recent times. This form of communication involves light; that neurons, indeed all living cells, can generate light and may use this to send messages to each other. This phenomenon has been termed ultra-weak photon emission; more recently, the term biophotons has been used (Grass et al., 2004; Tang and Dai, 2014; Salari et al., 2015; Mothersill et al., 2019; Van Wik et al., 2020; Zangari et al., 2021). For the present group of authors - who have been using external light to stabilize and repair damaged or distressed neurons (i.e., to induce resilience) - it has become essential to understand the role of light in the normal functioning of neurons and then to understand how the external light we have been using interacts with neuronal communication by biophotons.

In this perspective, we discuss the idea that neurons can use biophotons to communicate with each other, informing on states of activity and homeostasis. We will consider also that they may use biophotons for repair, either self-repair or the repair of neighbors. We suggest that external light, namely photobiomodulation (the use of red to near infrared light on body tissues), engages this biophoton code of communication and repair between neurons and stimulates beneficial outcomes. To start, we will consider how neurons make biophotons, the intensity and the wavelengths involved, and then why they may do so in the first place, the evolutionary basis for such a phenomenon.

Many studies have reported that biophotons arise from the many metabolic processes that occur within the cell (Grass et al., 2004; Tang and Dai, 2014; Salari et al., 2015; Mothersill et al., 2019; Van Wik et al., 2020; Zangari et al., 2021). The main source of biophotons is thought to be the mitochondria, the organelles where most of these metabolic reactions take place. In particular, biophotons appear to result from the process of oxidative metabolism, the excitation and subsequent relaxation to a stable state of reactive oxygen species. The biophotons are likely to be absorbed by a number of chromophores within the cell, including porphyrin, flavinic, and pyridinic rings, lipid chromophores, aromatic amino acids and cytochrome c oxidase. This absorption - either by the same or neighboring (also called bystander) cells - can then lead to a change in electrical activity (Mothersill et al., 2019; Zangari et al., 2021). Microtubules are also suspected to play a role in this process, being involved in the intracellular transmission of the signal (Tang and Dai, 2014; Mothersill et al., 2019). There is a distinct delay, from the time of biophoton production to absorption, called delayed luminescence; the length of this delay provides key information about the functional status of the cell (Salari et al., 2015).

There are two striking features of biophotons. First, they are emitted with a rather broad range of wavelengths, from ultraviolet to red and near infrared range (i.e., 200–950 nm). Such a broad range opens the possibility that particular wavelengths within that range are associated with different cellular reactions and different states of homeostasis (Dotta et al., 2014; Tang and Dai, 2014). Second, this self-generated light from neurons is not bright, not something that is detectable by the naked eye, nor even a relatively sensitive radiometer, but only with an ultra-sensitive light detection device, such as a photomultiplier or with a very specific histological stain (Zangari et al., 2021). It has been estimated that the number of biophotons generated by a cell can vary anywhere between 2–200 photons/s/cm^2 (Tang and Dai, 2014; Salari et al., 2015). This level of emission appears to occur steadily, but the level is increased or decreased by an external stimulus for example, by electrical stimulation, thermal or mechanical stress, the application of neurotransmitters like glutamate or the addition of an anesthetic or tetrodotoxin. It should be noted that both the biophoton intensity and wavelength can vary depending on the particular state of homeostasis of the cell. For example, there are distinct differences in both the numbers and wavelengths of biophotons evident between cancerous and non-cancerous cells (Tang and Dai, 2014; Salari et al., 2015).

Why do neurons generate light and should it be surprising? Surprise always arises from expectations and neuroscientists have had to learn and re-learn to manage our expectations, lest we miss the obvious. The brain is the most energy-intensive organ of the body at rest. Though it forms ~2% of total body weight, the brain requires ten-fold that share of the cardiac output to keep functioning. And what the brain needs from all that blood is glucose and oxygen to fuel energy production. All our tissues generate heat when they are metabolically active and the blood that brings their nutrients spreads that heat throughout the body. Hence, there should be no surprise that the same metabolic processes of mitochondria that produce the energy currency of neurons (i.e., adenosine triphosphate) and some collateral heat, may also generate light, in the form of biophotons.

But does this biophoton emission remain a waste product, a collateral emission of metabolic cell activity not used for any useful purpose, or has it developed to serve a distinct function (Grass et al, 2004). We suggest the latter, that all neurons may have evolved to use biophotons as a means of communication and repair (see below). An analogy may be found in the way in which engineers, after designing internal combustion engines to power motor vehicles for travel, found that the engines produced large amounts of collateral heat; they used this heat subsequently for another purpose, namely to provide heating for the cabin of the vehicle, for the comfort of passengers.

Although the precise function of biophotons is not entirely clear at present, we will focus on two possible actions. First, biophotons may form a major means of communication between neurons. Biophotons emitted by one neuron may inform bystander neurons of their activity state and whether they are functioning normally or are damaged (**Figure 1**). Their emission could for example, influence many intracellular functions, including mitochondrial activity and energy production, ion channel stimulation and/or permeation at molecular binding sites. This form of communication can be expressed by biophotons using a considerable spectral range (200–950 nm) and different patterns of intensity (i.e., number of biophotons) (Grass et al., 2004; Liebert et al., 2014; Tang and Dai, 2014; Salari et al., 2015; Mothersill et al., 2019; Van Wik et al., 2020; Zangari et al., 2021).

Is there any directionality to this state-of-the-neuron communication? There is evidence that communication by biophotons flows preferentially (but not exclusively) along the many known axon pathways of the brain, pathways that link large numbers of neurons together over considerable distances (**Figure 1**; Grass et al., 2004; Tang and Dai, 2014). In particular, the neurons associated with the amine pathways, including pathways using dopamine, serotonin or noradrenaline, appear most closely linked with biophoton emission and fluorescence (Tang and Dai, 2014; Mothersill et al., 2019). In addition to this flow along structural pathways, there appears to be some penetration of biophotons across the extracellular matrix (**Figure 1**). It is not clear what distances are involved here, but it is tempting to speculate that there is a biophoton code of communication between neurons that is not restricted by a set pathway or synaptic connectivity, one that may involve many neurons across, for example, an entire cerebral lobe. This mode of communication would be near-instantaneous and would require little energy, since it may use the collateral emission of light by major metabolic pathways (Tang and Dai, 2014).

Second, neurons, when damaged or in distress, may use biophotons as a means of repair, either for themselves or for bystanders (**Figure 1**), inducing repair of membranes, re-establishment of homeostasis, resumption of normal cell function (e.g., red to infrared), as well as inducing cell growth and division (e.g., ultraviolet: Dotta et al., 2014; Hamblin, 2016).

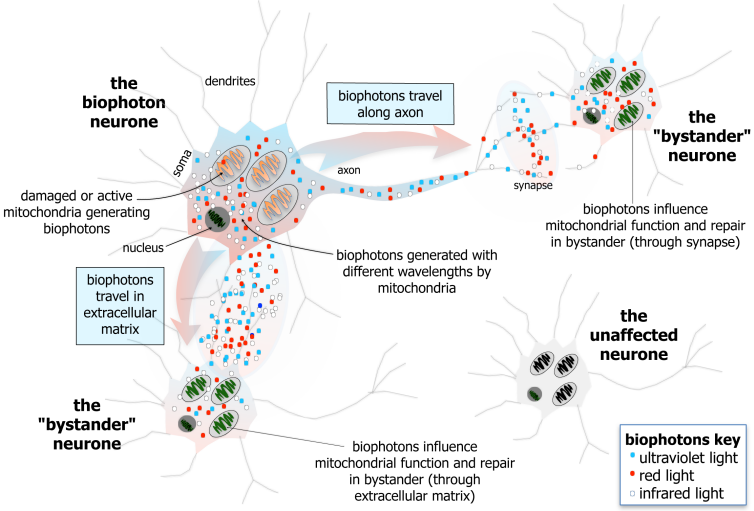

Figure 1 | Schematic diagram outlining the potential modes of biophoton network communication and repair among neurons.
If a neuron is very active or damaged (i.e., the biophoton neuron), its mitochondria may communicate with other neurons (the bystander neurons) through either axonal pathways and resulting synapse or through the extracellular matrix. The biophoton neuron, if damaged, may also use biophotons to repair itself and bystander neurons. Neurons that are not linked synaptically to the biophoton neuron nor in a surrounding region (through extracellular matrix) would remain unaffected (the unaffected neuron). Note that biophotons have a broad range of wavelengths, from ultraviolet to red to infrared (see key).

An issue worthy of some comment is whether external environmental light can influence the biophoton network between neurons (Grass et al., 2004; Tang and Dai, 2014). Nearly all neurons, particularly those of the central nervous system, are encased in bone (cranium and vertebral column) and thick connective tissue coverings (meninges). They work, for the most part, in near total-darkness. In these regions, communication by biophotons may be little influenced by external light. But there are some notable exceptions. The neurons of the retina, as well as peripheral sensory neurons innervating the skin are exposed continually to light and these neurons, unlike those that work in the dark, could have their biophoton network compromised. There is evidence however, that the communication by biophotons still operates within these light-exposed neurons. It appears that these, perhaps all, neurons may have developed a means of incorporating any external light exposure as part of their working biophoton system of communication and repair (Wang et al., 2011; Tang and Dai, 2014). Indeed, most previous work on biophotons has been on non-neuronal cells and most of these cells – whether from plant or animal – are exposed to external light continually (Grass et al., 2004; Tang and Dai, 2014; Salari et al., 2015; Mothersill et al., 2019; Van Wik et al., 2020). Hence, it is likely that any given living cell can operate a biophoton network with or without external light exposure.

In this context, many of the beneficial effects on cell function and survival provided by photobiomodulation, the application of red to near infrared light (λ = 600–1000 nm) on body tissues, may depend on the biophoton network (Liebert et al., 2014). Photobiomodulation, when applied to a living cell, stimulates mitochondrial activity and improves function and survival (Hamblin, 2016), just as biophotons of similar wavelengths would do, albeit at much lower intensities, after being emitted from either the same or bystander cells. This feature would explain, at least in part, the findings that neurons located so deep within the near total-darkness of the brain, are receptive to light and benefit from photobiomodulation. That is because they themselves use light - at very low intensity - to communicate and maintain homeostasis and photobiomodulation has its effects by engaging this network (Liebert et al., 2014).

In conclusion, there is a still-growing body of evidence that neurons self-generate light across a range of wavelengths, from ultraviolet to red and near infrared; and that this light, referred to as biophotons, has during evolution become a means of communication between neurons, informing each other on their different states of activity and homeostasis. Biophotons may also be used for repair when the neuron is damaged or in distress, either for itself or for others. We suggest that the beneficial effects of photobiomodulation pivot on engaging this biophoton communication and repair network. Although there is so much that remains unclear of how and why biophotons are produced, as well as their precise functional significance, the therapeutic implications of de-coding the biophoton communication and repair network are enormous. Technically, the development of an ultrasensitive biophoton detection device that identifies mitochondrial pathology in distressed and/or damaged neurons of the living human brain and then guides therapeutic intervention (e.g., targeted photobiomodulation) would be a goal worthy of much endeavor and exploration.

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Date of submission: June 9, 2021
Date of decision: July 16, 2021
Date of acceptance: August 9, 2021
Date of web publication: November 12, 2021

https://doi.org/10.4103/1673-5374.327332
How to cite this article: *Moro C, Liebert A, Hamilton C, Pasqual N, Jeffery G, Stone J, Mitrofanis J (2022) The code of light: do neurons generate light to communicate and repair? Neural Regen Res 17(6):1251-1252.*

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C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y