Ageing Research Reviews 53 (2019) 100913

Contents lists available at ScienceDirect

Ageing Research Reviews

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

Review

Effects of light on aging and longevity

Jie Shen[a,*], John Tower[b]

[a] College of Life Information Science & Instrument Engineering, Hangzhou Dianzi University, Hangzhou, 310018, China
[b] Molecular and Computational Biology Program, Department of Biological Sciences, University of Southern California, Los Angeles CA 90089-2910, United States

ARTICLE INFO

Keywords:
Aging
Circadian rhythms
Light
Phototherapy
Mitochondria
Oxidative stress

ABSTRACT

Increasing evidence suggests an important role for light in regulation of aging and longevity. UV radiation is a mutagen that can promote aging and decrease longevity. In contrast, NIR light has shown protective effects in animal disease models. In invertebrates, visible light can shorten or extend lifespan, depending on the intensity and wavelength composition. Visible light also impacts human health, including retina function, sleep, cancer and psychiatric disorders. Possible mechanisms of visible light include: controlling circadian rhythms, inducing oxidative stress, and acting through the retina to affect neuronal circuits and systems. Changes in artificial lighting (e.g., LEDs) may have implications for human health. It will be important to further explore the mechanisms of how light affects aging and longevity, and how light affects human health.

1. Effects of invisible light on aging and longevity

Light is an important environmental factor that affects living organisms, including regulation of circadian rhythms, metabolic rate and growth [Northrop, 1925; Tucker, Petitclerc et al. 1984; Sheeba, Sharma et al. 2000; Vinogradova, Anisimov et al. 2009]. The wavelength of visible light is between 380–720 nm. Invisible light is divided into two types: infrared light with wavelength greater than 720 nm; and ultraviolet (UV) light with wavelength less than 380 nm (Fig. 1).

1.1. UV light and aging

The effects of UV light on organisms have been extensively studied and well-reviewed [Amaro-Ortiz, Yan et al. 2014; Sanches Silveira and Myaki Pedroso, 2014; Lapierre, Kumsta et al. 2015]. UV light is mainly found to be harmful, but has shown beneficial effects in recent studies when used at moderate dose.

In non-mammalian model organisms, researches on UV showed negative effects. UVB and UVC directly damage DNA, by inducing the formation of DNA photolesions, often resulting in mutations. The two major classes of DNA lesions produced by UVB and UVC are cis-syn cyclobutane pyrimidine dimers and pyrimidine (6-4) pyrimidone photoproducts. The transcriptional status of the sequences and the chromatin environment are important for the repair of these photoproducts [Pfeifer, 1997]. The damaging effect of UVA possibly results from type II, oxygen-mediated photodynamic reactions, in which UVA enhances the production of reactive oxygen species (ROS) in the presence of photosensitizing chromophores such as nicotinamide adenine dinucleotide phosphate (NADPH), porphyrins or riboflavin [Dalle Carbonare and Pathak, 1992]. In this way, the UVA-generated ROS damages DNA, lipids, and proteins [Santos, Oliveira et al. 2013]. The lethal effects of UV irradiation on insects [Beard, 1972] and microorganisms[Reed, 2010] are well known, and therefore UV irradiation is used for killing pests and pathogens. There are also reports that UV irradiation decreases adult longevity in insects [Chang-Yu and Jian-Yu, 2011]. Administering high-energy UV light to *C. elegans* triggers an escape behavior, potentially allowing the animal to avoid further UV-mediated cellular damage [Ward, Liu et al. 2008], and also inhibits pharyngeal pumping [Bhatla and Horvitz, 2015].

In mammals, UV showed both positive and negative effects. UV radiation is the environmental mutagen associated with the largest percentage of environmentally induced skin pathologies, such as erythema and inflammation, degenerative aging changes, and cancer [Elwood and Jopson, 1997]. However, moderate UV exposure could be beneficial for human health. For example, UVB irradiation promotes the generation of vitamin D in the skin [Bouillon, 2017]. There is also a recent study showing that moderate UVB exposure on mice improves motor learning and object recognition memory, by elevation of urocanic acid levels in blood and brain, and therefore promoting glutamate biosynthesis and release in specific brain regions [Zhu, Wang et al. 2018].

* Corresponding author at: College of Life Information Science & Instrument Engineering, Hangzhou Dianzi University, Hangzhou, 310018, China.
E-mail address: shenjie@hdu.edu.cn (J. Shen).

https://doi.org/10.1016/j.arr.2019.100913
Received 23 March 2019; Received in revised form 17 May 2019; Accepted 29 May 2019
Available online 30 May 2019

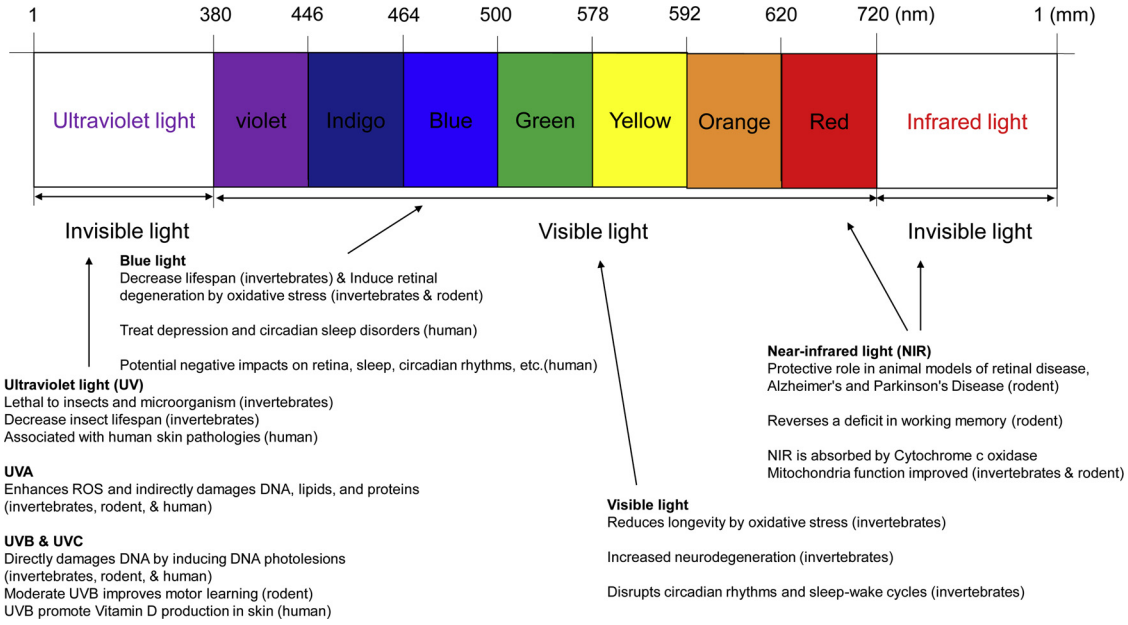

Fig. 1. The wavelengths of visible light, ultraviolet light, infrared light, and their effects on aging.
As indicated in the figure, the wavelength of visible light is between 380–720 nm; ultraviolet light is less than 380 nm; infrared light is greater than 720 nm. The effects on aging of ultraviolet light (UV), near-infrared light (NIR), blue light, and visible light are listed briefly in the figure, and explained in further detail in the text.

1.2. NIR and aging

Different from UV, the effect of near-infrared light (NIR) is beneficial. NIR has shown some protective effects in several animal models of retinal disease [Begum, Powner et al. 2013; Calaza, Kam et al. 2015], Alzheimer's Disease and Parkinson's Disease [Peoples, Spana et al. 2012; Johnstone, Moro et al. 2015], and can reverse the deficit in working memory in middle-aged mice [Michalikova, Ennaceur et al. 2008], possibly by improving mitochondrial function and ATP production [Begum et al., 2015; Calaza, Kam et al. 2015]. Cytochrome c oxidase (COX), which is the terminal enzyme of the respiratory chain on the membrane of mitochondria, is identified as the photoacceptor of the NIR photobiomodulation effects. COX mediates the transfer of electrons from cytochrome c to molecular oxygen, and the reactivity of COX is due to four redox active metal centers: the binuclear CuA, CuB, heme a and heme a3. Analysis of action spectra of living cells in various experimental conditions showed that the peak profiles are similar to absorption spectra of redox metal centers of COX [Karu, 2013]. When NIR is absorbed by COX, the redox state of COX changes, to cause the increase in ATP, decrease in both ROS and inflammation, and improved mitochondria function [Begum et al., 2015]. NIR elements are produced by older domestic incandescent or halogen lighting (Fig. 2, spectrum of LED vs halogen lights), but are not present in fluorescent lighting or LED lighting [Begum, Powner et al. 2013]. The change of artificial lighting may have significant impact on aging and health.

In the indoor working environment, and in the animal culture research environment, fluorescent lighting and LED lighting are most common. Humans and research organisms are typically exposed to a mix of spectrum of visible light. In this review, we focus on the effects of visible light on aging and longevity.

2. Effects of visible light on aging and longevity

2.1. Visible light and aging

Visible light from ambient lighting can be toxic and reduce longevity. A recent study showed that visible light can reduce longevity in *C. elegans* [De Magalhaes Filho, Henriquez et al. 2018]. The effect of light was photon energy dependent, and lifespan was inversely correlated to the time that the *C. elegans* were exposed [De Magalhaes Filho, Henriquez et al. 2018]. Consistent with the result in *C. elegans*, our recent study on *Drosophila* also showed that visible light could reduce longevity [Shen et al., 2018]. A previous analysis of different photoperiods showed that life span of *Drosophila* in constant light (LL) is significantly shorter when compared with alternating light-dark cycles (LD 12:12 h), and constant darkness (DD) [Massie, Aiello et al. 1993].

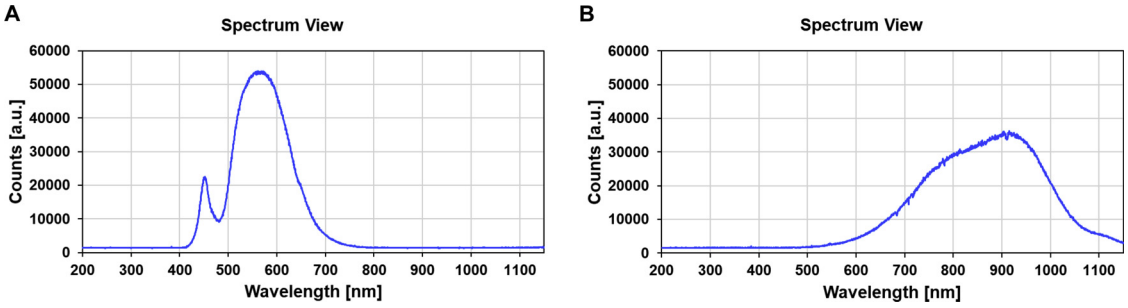

Fig. 2. Wavelength spectrum of LED and halogen lights.
Spectrum views measured by a spectroscope. The x axis represents the wavelength distribution of the light. The y axis "Counts (a.u.)" means arbitrary units of light intensity, which represents the relative intensity of light (relates to watt). A, Spectrum view of white LED light. B, Spectrum view of white halogen light.

The recent study in *C. elegans* is consistent with those observations, showing longest life span under constant darkness (DD) condition but shortest life span under constant light (LL) condition [De Magalhaes Filho, Henriquez et al. 2018]. Further study of the mechanism in *C. elegans* showed that oxidative stress and unfolded-protein response, but not circadian rhythms, contribute to the reduction of lifespan, as antioxidants feeding could rescue the lifespan reduction caused by visible light [De Magalhaes Filho, Henriquez et al. 2018]. In *Drosophila*, oxidative stress is also a possible mechanism for the toxic effects of visible light. A previous study of photosensitizers and aging showed that the photosensitizer, methylene blue decreased lifespan, suggesting that photodynamic action, in which the energy of visible light is transferred to the photosensitizer and then in turn transferred to molecular oxygen, may be the mechanism [Massie, Aiello et al. 1993]. In a fly model of Alzheimer's disease, exposure to dim light of 10 lx at night, which is considered the lower limit of light pollution, increased phosphorylated Tau protein abundance and neurodegeneration, and disrupted circadian rhythms and sleep-wake cycles [Kim, Subramanian et al. 2018]. Studies in rodents showed similar toxic effect of visible light. Rats exposed to 90 days' continuous bright light from a fluorescent lamp showed increased numbers of neuromelanin-positive neurons, decreased TH-positive neurons in the substantia nigra (SN) region, and reduction of dopamine levels [Romeo, Viaggi et al. 2013]. Consistent with that observation, three months' fluorescent light exposure to mice caused reduction of dopamine neuron numbers, and reduced levels of dopamine [Romeo, Vitale et al. 2017]. A possible mechanism is that light exposure induced dopamine oxidation which in turn led to increased apoptosis.

2.2. Blue light and aging

Blue light (400–500 nm, short-wavelength visible light) has shown toxic effects that can contribute to aging. Blue light significantly decreased adult longevity of *Drosophila melanogaster* [Hori, Shibuya et al. 2014]. The effects of blue light were photon-dose dependent, and flies kept under dark conditions showed the longest mean lifespan. The wavelength of blue light with most toxicity relies on the developmental stage and photon dose [Shibuya, Onodera et al., 2018]. The toxic effects of blue light may be caused by ROS and oxidative stress [Hori, Shibuya et al. 2014; Shibuya, Onodera et al. 2018]. Blue light exposure could induce lipid peroxidation which contributed to retinal degeneration in -6-day-old *Drosophila melanogaster*. The membranes of photoreceptors in the eye are rich in peroxidation-susceptible polyunsaturated fatty acids, and overexpression of cytochrome b5 (Cyt-b5) prevented lipid peroxidation and retinal degeneration caused by blue light. The possibly mechanism could be that Cyt-b5 enhance the regeneration of antioxidant coenzyme Q in the cells and thus promotes the recycling of vitamins C and E [Chen, Hall et al. 2017].

2.3. Long-wavelength visible light and aging

On the other hand, long-wavelength visible light has shown beneficial effect on aging. Long-term exposure to 670 nm in *Drosophila melanogaster* increased ATP levels, reduced inflammation, and significantly increased mean lifespan and mobility in old age [Begum et al., 2015]. Old flies exposed to 670 nm daily for one week showed significantly improved retinal function, cognitive ability and mobility. The beneficial effect of 670 nm light appears to be mediated by improved mitochondria function, as indicated by increased ATP levels, mitochondrial DNA content, cytochrome c oxidase activity, and whole body energy storage [Weinrich, Coyne et al. 2017].

3. Effects of visible light on human health

3.1. Mechanisms for adaptation to light in humans

Human adaptation to ambient light has two mechanisms: image forming (IF) for vision, and non-image forming (NIF). NIF functions are mediated by retinal ganglion cells (RGCs) expressing the photopigment melanopsin, and the action spectrum of melanopsin photopigment peaks around 480 nm blue light [Hatori, Gronfier et al. 2017]. Action spectrum shows which wavelength of light is most effectively used in a physiological reaction, by plotting the rate of the reaction versus input wavelength [Karu, 2013]. By testing phototransduction sensitivity to monochromatic stimuli at different wavelengths, the action spectrum of melanopsin was measured with peak sensitivity around 480 nm. The action spectrum of RGCs, which contains melanopsin, also peaks around 480 nm, and is consistent with peak sensitivity of NIF photoresponses such as circadian photoentrainment. The action spectrum is different from the excitation spectrum, which shows the relationship of the substance's radiation wavelength with the external excitation light wavelength. NIF responses vary widely from pupil diameter adjustment to adaptation of the circadian clock. Therefore, NIF is important in aging and age-related disorders, by regulation of circadian rhythmicity.

Since the invention of the incandescent light bulb in the 19th century, halogen light bulbs and fluorescent lamps in the 20th century, and light-emitting diode (LED) in the 21 st century, the easy access to light changed human lifestyle. The revolution of LED lighting saves energy, but also delivers a much higher amount of blue light compared to conventional light sources [Hatori, Gronfier et al. 2017].

3.2. The beneficial and harmful effects of blue light

Blue light has negative effects on human health but can also be used to treat human diseases when used at appropriate dose. Moderate blue light may be beneficial to humans and work as an effective "bright light therapy" in treating depression and circadian sleep disorders [Czeisler, 2013; Lam, Levitt et al. 2016]. But there are also concerns about the negative effects of blue-rich light on human health, such as potential negative impacts on the retina, sleep, non-visual/circadian biology, cancers, obesity, diabetes, and psychiatric disorders [Stevens, Brainard et al. 2013; Bonmati-Carrion, Arguelles-Prieto et al. 2014].

3.3. The amount of sunlight and human diseases

A lack or increase of sunlight is correlated with certain diseases. For example, while the etiology of multiple sclerosis (MS) is not well known, epidemiologists have observed an increased prevalence of MS in countries at high latitudes with limited sunlight [Ghareghani, Reiter et al. 2018]. There is also a study showing that UV exposure can reduce MS risk [Gallagher, Ilango et al. 2018]. Seasonal affective disorder, a form of depression, shows a high frequency in high latitudes where light availability is decreased and therefore the amplitude and phase of circadian rhythms is blunted. Bright light therapy is a successful treatment to seasonal affective disorder due to limited light availability [Duncan, 1996; Gonzalez and Aston-Jones, 2008]. Sunlight may associate with suicide, possibly by interacting with serotonin neurotransmission [Vyssoki, Praschak-Rieder et al. 2012; Makris, Reutfors et al. 2016]. Increase in sunlight was found to be inversely related with the age of onset of bipolar disorder [Bauer, Glenn et al. 2014].

4. Possible mechanisms of light effects on aging

4.1. Circadian rhythm disturbance

Changes in circadian rhythms may explain the effect of light on aging. One mechanism of the light function is to act as a zeitgeber (time giver), to control the circadian rhythms, which are endogenous rhythms of about 24 h. With circadian rhythms, organisms can synchronize their physiology with the daily light-dark phase change of Earth's rotation. Although light is a zeitgeber to circadian rhythms, in constant darkness (free running conditions), the rhythms still exist and can be reset by exposure to external signals including light. In humans, night time

exposure to light could cause disturbances in circadian rhythms. Night shift work or chronic jet lag experience may have a negative effect on obesity, diabetes, and cancer incidence [Haus and Smolensky, 2013; Zelinski, Deibel et al. 2014; West and Bechtold, 2015]. In addition, disruption of the circadian clock may accelerate physiological aging. In mice, the null mutation in the core clock gene Bmal1 (homolog of cyc) significantly shortened lifespan [Kondratov, Kondratova et al. 2006]. Disruption of the core clock genes has also been shown to affect the lifespan of *Drosophila*. In per mutants, *Drosophila* lifespan was reduced [Klarsfeld and Rouyer, 1998]. In cyc-null male but not female flies, shortened lifespan was also observed [Hendricks, Lu et al. 2003]. Overexpression of tim in peripheral tissues extended lifespan under ad libitum conditions, by increasing fat metabolism [Katewa, Akagi et al. 2016]. In addition, *per*-null mutants also showed impaired health span, as indicated by reduced oxidative stress resistance and climbing ability, higher oxidatively damaged proteins and lipids [Krishnan, Kretzschmar et al. 2009].

4.2. Oxidative stress induction by light

Another mechanism of light is to cause oxidative stress which is circadian rhythm-independent. Light was found to drive the expression of a large number of non-circadian genes. These genes are not true circadian genes because they do not continue rhythmic cycle changes in constant darkness (free running conditions) [van der Linden et al., 2010]. As discussed above, a recent study in *C. elegans* showed that the reduction of lifespan by visible light is due to oxidative stress, and antioxidants can rescue the shortened lifespan [De Magalhaes Filho, Henriquez et al. 2018]. Other studies also support that light induces oxidative stress and damages lipids, proteins and DNA [Kuse, Ogawa et al. 2014; Chen, Hall et al. 2017]. Mammalian hepatocytes under visible light exposure showed photodamage, such as inactivation of catalase and inactivation of lysosomal enzymes [Cheng and Packer, 1979]. Even light sources with limited UV or blue light (short wavelength) components could cause significant oxidative stress. Incandescent light (which lacks UV and most of the blue wavelengths) can produce pyrimidine dimers in DNA [Ciarrocchi, Sutherland et al. 1985]. Three hours of fluorescent light at 1000 lx can induce significant DNA strand breaks in mammalian cells [Bradley, Erickson et al. 1978].

4.3. Signal transduction through the visual system

Finally, light may function through the retina to affect neuronal circuits and systems. Blue light (short wavelength) has the highest photon energy in the visible spectrum, and can cause retinal damage, called “blue light hazard” [Buczylko, Saari et al. 1996, Maeda, Maeda et al., 2009; Chen, Okano et al. 2012; Maeda, Golczak et al. 2012; Zhong, Kawaguchi et al. 2012]. A study in mice showed that blocking blue light protects the retina from light damage [Narimatsu, Ozawa et al. 2014]. The photoreceptor chromophore retinal can enter the circulation, and therefore, retinal can confer light sensitivity to both visual and non-visual cells. Retinal can induce distortions in PIP2, cause oxidative stress, and cause increase in cytosolic calcium levels [Ratnayake, Payton et al. 2018]. In aged flies, phototaxis and oscillation of electroretinograms (ERGs) are greatly reduced [Ueda, Woods et al. 2018]. In the aging process, the damage of the retina by light could be cumulative, and lead to a decline in neuronal excitability and synaptic transmission.

5. Discussion and conclusions

Light exposure is an environmental factor that significantly impacts aging and longevity. Light intensity, spectral components, and duration of exposure, are all important factors to consider when conducting animal experiments. Light conditions should be carefully controlled to avoid potential conflicts between different studies.

There is no uniform measurement unit for intensity of light in research papers. Lux, photons, and Watts are all used in published research studies. The commonly used “lux” indicates the intensity of light perceived by human eyes, which are most sensitive to yellow and green light, even if the radiant energy of each color is equal. Therefore, lux can not accurately indicate the absolute energy of light, such as high energy blue light. For example, use of blue light in Seasonal Affective Disorder (SAD) therapy according to protocols which use lux to determine the light intensity, would be an over-dose [Anderson, Glod et al. 2009]. Photon flux(photons/cm2/sec) is another unit for light measurement. The photochemical reaction of photosynthesis is closely related to the number of absorbed light photons. For example, a photon of blue light has about twice the energy of a red light photon, but the photons of these two colors have the same effect in photosynthesis. Therefore, photon flux is commonly used to describe photosynthetically active radiation (400–700 nm) [Thimijan, 1983]. Watt reflects the total absolute radiated power of all electromagnetic radiation (including infrared, ultraviolet, and visible light) passing through a certain area per unit time. Therefore, watt would be the unit to make comparisons between different studies easier, although the intensities with different units can be converted by equations [Enezi, Revell et al. 2011]. It would be helpful to form a consensus on standard lighting conditions for aging experiments in the future.

It will also be important to further explore the mechanisms of how light affects aging and longevity. With the emergence of new lighting technologies, especially light-emitting diode (LED), future research needs to focus on the impact of different light sources on human health and disease. The future of research on light and aging could be:

- What are the effects of light of various wavelengths and intensities on aging and longevity?
- How do circadian rhythms interact with the effect of light on aging?
- What are the detailed mechanisms of oxidative stress in response to light? How could the harmful effects be prevented?
- What is the role of the retina in the different effects of light?
- Does the microbiome correlate with the effects of light at specific wavelengths?
- What light interventions can be developed to help treat aging-related diseases, such as AD and PD?
- Would any dietary component (e.g. protein) or dietary supplement (e.g. photo-sensitizing substance) enhance the beneficial effect or reduce the toxic effect of light?

In conclusion, light is a ubiquitous and important regulator that affects aging. Further research on the detailed mechanisms of light would be helpful for researchers to set optimal consensus lighting conditions for research, and to develop noninvasive lighting therapies for aging-related diseases.

Acknowledgements

The authors declare no conflicts of interest. This work was supported by grants to J.S. (National Natural Science Foundation of China, 31500970) and to J.T. (NIH/NIA AG057741).

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