Abstract

Sleep is a critical part of our daily routine. It impacts every organ and system of our body, from the brain to the heart and from cellular metabolism to immune function. A consistent daily schedule of quality of sleep makes a world of difference to our health and well-being. Despite its importance, so many individuals have trouble sleeping well. Poor quality sleep has such a detrimental impact on many aspects of our lives; it affects our thinking, learning, memory, and movements. Further, and most poignantly, poor quality sleep over time increases the risk of developing a serious medical condition, including neurodegenerative disease. In this review, we focus on a potentially new non-pharmacological treatment that improves the quality of sleep. This treatment, called photobiomodulation, involves the application of very specific wavelengths of light to body tissues. In animal models, these wavelengths, when applied at night, have been reported to stimulate the removal of fluid and toxic waste-products from the brain; that is, they improve the brain’s inbuilt housekeeping function. We suggest that transcranial nocturnal photobiomodulation, by improving brain function at night, will help improve the health and well-being of many individuals, by enhancing the quality of their sleep.

Key Words: aquaporin 4; glymphatic; infrared; non-pharmacological; red; sleep cap; transcranial; wakefulness

Introduction

The brain is considered to have two quite distinct operative states. The first is the state of wakefulness, the so-called “day-time brain”. In this state, the brain is in a conscious mode, being receptive to, and interactive with, the environment. It is engaged fully with the generation and orchestration of complex neural circuitry associated with the executive functions, such as focusing attention, being cognitively active, encoding memories, and undertaking skilled movements. Each of these brain functions deals with the many challenges and events faced by individuals daily.

The second is the state of sleep, the so-called “night-time brain”. In this state, the brain is in an unconscious, but arousable mode and is far less receptive to the environment (Rash and Born, 2013; Eugene and Masiak, 2015). Although the precise function of sleep remains a mystery, notwithstanding the considerable amount of time and effort invested by both scientists and philosophers over many centuries, there is recent evidence indicating that it is associated with a house-keeping function. This function involves the disposal of all the metabolic debris and waste-products that have accumulated in the brain during the day; there is a “cleaning of the house”, so to speak. These waste-products need to be cleared; otherwise, they accumulate and become toxic. The brain undertakes this house-keeping function largely by using a flow of fluid that sweeps across the spaces between its constituent neural cells, taking all the waste-products with it, draining ultimately into the venous system. This house-keeping function is not, in fact, too far removed from Aristotle’s original idea, all those centuries ago, that sleep serves to help filter, cleanse and refresh the body and brain (Iliff et al., 2012; Rash and Born, 2013; Aspelund et al., 2015; Eugene and Masiak, 2015; Jessen et al., 2015; Loveau et al., 2015, 2017; Brodziak et al., 2018; Hablitz et al., 2020; Mestre et al., 2020; Nedergaard and Goldman, 2020; Reddy and van der Werf, 2020; Yan et al., 2021).

In the section that follows, we consider the sleeping brain and its house-keeping function. We will then focus on how the brain undertakes this house-keeping function, exploring the system and the mechanisms involved. Next, we discuss the method of photobiomodulation - the application of very specific wavelengths of light to body tissues - and its impact on the brain at night and during sleep. Finally, we will highlight the idea that photobiomodulation may form an effective, non-pharmacological treatment that improves the quality of sleep and hence the health and well-being of many individuals.

The Sleeping Brain and the House-Keeping Function

The house-keeping function of the brain has been considered to be reserved largely for the state of sleep (Iliff et al., 2012; Rash and Born, 2013; Aspelund et al., 2015; Eugene and Masiak, 2015; Jessen et al., 2015; Loveau et al., 2015, 2017; Brodziak et al., 2018; Hablitz et al., 2020; Mestre et al., 2020; Nedergaard and Goldman, 2020; Reddy and van der Werf, 2020; Yan et al., 2021). The brain cannot readily fulfill this house-keeping during wakefulness, while it is undertaking so many complex higher-order executive functions involving billions of precise synaptic connections. It would be counterproductive to have waves of fluid, filled with toxic waste-products, flowing through it simultaneously; some of these waste-products would include, for example, excess neurotransmitters (e.g., glutamate) that may well stimulate unwanted activity in surrounding synapses (Nedergaard and Goldman, 2020).

In this context, the ascending neurotransmitter systems that are active during wakefulness (e.g., noradrenaline) tend to suppress the drainage and clearance of fluid within the brain; with a reduction of these neurotransmitter systems during sleep, the fluid clearance system of the brain is resumed (Constantinople and Bruno, 2011). It should be noted that day-time sleep (e.g., cat-nap or siesta) is generally much lighter than night-time sleep, presumably because it is not aligned with the house-keeping function (Iliff et al., 2012; Rash and Born, 2013; Aspelund et al., 2015; Eugene and Masiak, 2015; Jessen et al., 2015; Loveau et al., 2015, 2017; Brodziak et al., 2018; Hablitz et al., 2020; Mestre et al., 2020; Nedergaard and Goldman, 2020; Reddy and van der Werf, 2020; Yan et al., 2021).

There are two main types of sleep (Dijk, 2009; Rash and Born, 2013; Eugene and Masiak, 2015). The first type is referred to as slow-wave, non-rapid eye movement (nREM) sleep and is characterized by slow-wave, high-amplitude oscillations; it is very much reflective of a state of rest. This type of sleep can be divided into three main stages, namely stages 1, 2, and 3. Stage 1 is considered to be the transition between wakefulness and sleep; stage 2 is considered light sleep where muscle relaxation occurs, heart rate slows, and temperature drops; and stage 3 is deep sleep, characterized by the predominance of the slow-wave forms (e.g., 6 and 9 waves). The second main type of sleep is referred to as paradoxical, rapid eye movement (REM) and is characterized by fast-wave, low-amplitude oscillations (e.g., α and β waves). In this type of sleep, most of our dreams occur and the brain is just as active,
If individuals are deprived of quality sleep—that is, adequate periods of slow-wave sleep (Dijk, 2009)—and the brain does not clear its waste-products effectively, then many negative consequences may develop; for example, during the day, individuals are generally less attentive, have a slower cognitive function and memory, and may have problems with motor functions. In essence, the higher-order executive brain functions are diminished (Iliff et al., 2012; Aspelund et al., 2015; Jessen et al., 2015; Loveau et al., 2015, 2017; Brodziak et al., 2018; Hablitz et al., 2020; Mestre et al., 2020; Nedergaard and Goldman, 2020). Second, there is a clear age-related decline in glymphatic activity, in both fluid inflow and clearance (Jessen et al., 2015; Loveau et al., 2015, 2017; Brodziak et al., 2018; Hablitz et al., 2020; Mestre et al., 2020; Nedergaard and Goldman, 2020; Reddy and van der Werf, 2020). If there is an abnormal accumulation of this protein, presumably due to a lack of efficient clearance by the glymphatic system, then it becomes toxic. β-amyloid has long been associated with the development and progression of Alzheimer’s disease (Ballard et al., 2011; Nelson and Tabet, 2015; Scheletens et al., 2016; Crous-Bou et al., 2017). Further, pretreatment of wild-type mice with β-amyloid leads to a suppression of fluid tracer influx, indicating that β-amyloid aggregation feed-forwards and generates a further reduction of glymphatic activity (Nedergaard and Goldman, 2020). Finally, in a mouse model of tauopathy, there is a clear dysfunction of glymphatic activity, in the particular flow of cerebrospinal fluid and aquaporin-4 polarization, with the use of an aquaporin-4 inhibitor (Harrison et al., 2020).

Fourth, linking closely with the last feature, there are indications that there is a relationship between the fluid flow and the occurrence of Alzheimer’s disease. Evidence that Photobiomodulation Helps the Garbage Disposal System of the Sleeping Brain

When taking together the findings from all these previous studies, it is clear that good quality sleep results in an efficient clearance of fluid and waste from the brain by the glymphatic system, leading ultimately to a better state of overall health and well-being. It also reduces the risk of developing a range of serious medical conditions, including cardiovascular and neurodegenerative diseases. It stands to reason then, that a stimulation and maintenance of an efficient glymphatic system would lead to better quality sleep for individuals together with improving their health and well-being, as well as helping to delay the onset of disease.

In this context, photobiomodulation, the application of red to near infrared light on body tissues, has been shown recently to improve the clearance of fluid and toxic substances from both the periphery and from the brain (Figure 1C; Yue et al., 2019; Zinchenko et al., 2019; Semyachkina-Glushkova et al., 2021). In particular, photobiomodulation (λ=1267 nm) prompts the clearance of fluid through the glymphatic system, through a relaxation of lymphatic vessels, presumably
after a photobiomodulation-induced release of nitric oxide, together with an increase in the permeability of lymphatic endothelium (e.g., Semyakhina-Glushkovskaya et al., 2021a). In the brain, photobiomodulation leads to an improved clearance of experimentally-introduced substances, for example, gold nanorods and dextran, into the cerebrospinal fluid (Semyakhina-Glushkovskaya et al., 2020). Further, and most importantly, photobiomodulation has been shown to reduce β-amyloid brain accumulation and cognitive behavior of Alzheimer’s-induced mice more effectively during sleep, than during wakefulness (Semyakhina-Glushkovskaya et al., 2021b). It also reduces β-amyloid deposition in the interstitial space and stimulates the overall flow of interstitial fluid, as well as inducing the break-up of β-amyloid assemblies and activating enzymes that reduce β-amyloid aggregation (A = 630 nm; Yue et al., 2019). In addition, photobiomodulation when applied to normal mice prompts a much faster clearing of β-amyloid from the lateral ventricle of the brain down to the deep cervical lymph nodes at night, than during the day (Semyakhina-Glushkovskaya et al., 2021b).

Finally, photobiomodulation (A = 1267 nm) has been shown to stimulate the clearance of fluid within the lymphatic vessels of the meninges; the efficacy of these delicate vessels is crucial in clearing β-amyloid away from the brain (Zinchenko et al., 2019).

The precise photobiomodulation-induced mechanisms that underpin the improved fluid clearance and disposal of waste-products of the sleeping brain are not clear. Several have been suggested, however. For example, the ability to break down protein aggregations and to stimulate vasodilation, at least within the meningeal lymphatic vessels, after a release of nitric oxide, may be a contributing factor (Yue et al., 2019; Zinchenko et al., 2019; Semyakhina-Glushkovskaya et al., 2020, 2021a,b; Salehpour et al., 2022). Photobiomodulation may also impact the composition of cerebrospinal fluid, by changing the structure of the water molecules, making the fluid less viscous and freer flowing (Salehpour et al., 2022). In addition, the heat generated from an extracranial photobiomodulation device (see below) may create a temperature gradient encouraging the flow of cerebrospinal fluid through the brain (Salehpour et al., 2022). It is likely that many other, currently unknown, mechanisms are at play also. In particular, the mechanisms behind the photobiomodulation-induced stimulation of the glymphatic system remain to be determined. We speculate, however, that photobiomodulation may work primarily to increase the permeability of the aquaporin-4 water channels on the astrocytes, thereby helping to increase the flow of fluid through the brain.

It should be noted that the range of wavelengths of light considered as “photobiomodulation” (ie, λ = 600–1000 nm) has not been shown to suppress the brain release of melatonin, the key hormone in maintaining circadian rhythm and sleep. In fact, these longer wavelengths have even been suggested to promote the release of melatonin, which can only be of benefit to a better night’s sleep (Yakeger et al., 2007). Further to this point, photobiomodulation has been reported to induce sleeping and prolong sleep duration in mice (Zhang et al., 2017). Blue light (A = 380–500 nm), by contrast, has the reverse effect by suppressing melatonin release and prolonged night-time exposure results in a poor quality of sleep (Wahl et al., 2019).

The stage is set for the development of a photobiomodulation device that works at night, on the sleeping brain. Although many pharmacological interventions work to improve the length of sleep, many individuals either do not respond to the drugs available and/or prefer to use a non-pharmacological option. Such a non-pharmacological option, like photobiomodulation, would hence be of enormous benefit to many individuals across the wider community. Although there are a large number of extracranial “helmet” devices available on the market delivering photobiomodulation to the brain, for example, the well-red coronet (www.wellfred.com.au) and vielight (www.vielight.com), these devices have been designed to work on the brain during waking hours, but not at night-time, during sleep. The daytime devices serve to improve the executive functions in healthy individuals, together with those suffering from a neurodegenerative disease (e.g., Alzheimer’s or Parkinson’s disease), traumatic brain injury, or stroke (Hamblin, 2016; Mitrofanis, 2019). A night-time device may work on different systems, for example, stimulating the glymphatic system, helping improve sleep and overall well-being.

Conclusions

Sleep is such a critical part of our daily and periods of poor quality sleep can affect severely our normal day-to-day functioning. When these periods of poor sleep become more long-term, there is an increased risk of developing a serious medical condition, like a cardiovascular or neurodegenerative disease. Recent studies in animal models have shown that photobiomodulation improves the function of the brain during sleep; that it stimulates the removal of toxic waste products into the venous system. We suggest that nocturnal photobiomodulation, by stimulating the function of the glymphatic system of the brain at night, will form an effective non-pharmacological treatment that helps improve the overall quality of sleep, and hence well-being and long-term health of many individuals.

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