Mechanisms and Pathways of Pain Photobiomodulation: A Narrative Review

A growing body of evidence supports the modulation of pain by light exposure. As such, phototherapy is being increasingly utilized for the management of a variety of pain conditions. The modes of delivery, and hence applications of phototherapy, vary by wavelength, intensity, and route of exposure. As such, differing mechanisms of action exist depending upon those parameters. Cutaneous application of red light (660 nm) has been shown to reduce pain in neuropathies and complex regional pain syndrome-I, whereas visual application of the same wavelength of red light has been reported to exacerbate migraine headache in patients and lead to the development of functional pain in animal models. Interestingly visual exposure to green light can result in reduction in pain in variety of pain conditions such as migraine and fibromyalgia. Cutaneous application typically requires exposure on the order of minutes, whereas visual application requires exposure on the order of hours. Both routes of exposure elicit changes centrally in the brainstem and spinal cord, and peripherally in the dorsal root ganglia and nociceptors. The mechanisms of photobiomodulation of pain presented in this review provide

a foundation in furtherance of exploration of the utility of phototherapy as a tool in the management of pain.

The exposure of human biological systems to light is ubiquitous. Importantly, light exposure from the sun determines much of human circadian rhythms and behavior. Sunlight at dawn promotes biological effects including waking, increases in glucocorticoid secretion, and feeding.[7] In the modern-day era, however, exposure to light is not limited to sunlight exposure. Artificial indoor lighting and computers present in the workplace and home contribute a significant amount of light exposure.[28,33] Human exposure to light has also increased at night, whether from street lights, night lights, or workplace lights due to night shift work.[14] These aberrant light exposures cause circadian rhythm disruptions that have been linked to negative health effects on mood, metabolism, immune defense, and cancer risk.[7] Needless to say, the exposure to light has many important implications on human biology and behavior.

The use of light in the form of phototherapy has been increasingly investigated, although the idea has historical precedent.[46] In the late 1800s, Nobel laureate Niels Ryberg Finsen reported the use of red light in the treatment of smallpox, as well as the use of ultraviolet light to treat lupus vulgaris.[73] Light of various colors and wavelengths has since been used to treat a wide variety of conditions, including

neonatal jaundice, seasonal affective disorder, acne, circadian rhythm disruptions, and psoriasis.[46] Recently, light has been reported to have an effect on pain, both as a treatment for pain as well as an aggravator of pain.[43,66,76,88,90]

In the United States alone, 50 million adults have chronic pain, with an estimated $261 to 300 billion dollars being spent yearly to manage pain, resulting in an annual economic cost of chronic pain of at least $560 to 635 billion.[18,44] Current methods of pain management involve pharmacotherapy using agents such as serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, corticosteroids, benzodiazepines, gabapentinoids, and opioids; however, the use of these drugs does not come without concerning side effects such as sedation, cardiotoxicity, ataxia, addiction, and respiratory depression.[27,98] Therefore, there has been a growing desire for research on complementary, nonpharmacological methods of pain relief therapies and management. Current nonpharmacologic therapies for pain include psychological, behavioral, meditative, and physical therapy approaches, as well as specialized procedural intervention techniques by pain specialists.[1,3,98] Recently, investigations into the use of light as a treatment for symptomatic pain and pain syndromes have become particularly attractive as they are considered a low-cost,

nonpharmacologic alternative with few side effects.

Studies on pain in relation to light administration have reported varying responses depending on the wavelengths, intensities, and routes of administration of light. For example, exposure to green light via the visual system resulted in lesser pain in an acute migraine episode compared to the exposure of other wavelengths such as white, blue, amber, and red.[76] Red light administered through visual pathways caused thermal hyperalgesia and mechanical allodynia in rats.[47] However, red light administered cutaneously decreased both thermal and mechanical hyperalgesia in a mouse model of complex regional pain syndrome.[90] These reports are just a few examples of the varying effects of light on pain. Many articles report light-induced analgesia as well as hyperalgesia, and novel studies have been conducted to tease out the mechanistic basis of the effects of light on pain.[39,43,66,78,81] Promising results in preclinical animal studies have led to the clinical translation of phototherapies for pain management. Although the underlying mechanisms have yet to be fully elucidated, the fact that light can modulate pain is increasingly being acknowledged with more experimental and clinical evidence forthcoming. This review strives to shed light on the effects of light on pain, the biological mechanisms through which light acts on pain, as well as the current applications of phototherapy on pain.