Medical Hypotheses 82 (2014) 275–281

Contents lists available at ScienceDirect

Medical Hypotheses

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

Protein conformational modulation by photons: A mechanism for laser treatment effects

Ann D. Liebert [a], Brian T. Bicknell [b], Roger D. Adams [a,*]

[a] Faculty of Health Sciences, University of Sydney, Australia
[b] Faculty of Health Science, Australian Catholic University, Australia

ARTICLE INFO

Article history:
Received 3 September 2013
Accepted 15 December 2013

ABSTRACT

Responsiveness to low-level laser treatment (LLTT) at a wavelength of 450–910 nm has established it as an effective treatment of medical, veterinary and dental chronic pain, chronic inflammation conditions (arthritis and macular degeneration), wound repair, and lymphoedema, yet the mechanisms underlying the effectiveness of LLLT remain unclear. However, there is now sufficient evidence from recent research to propose an integrated model of LLLT action. The hypothesis presented in this paper is that external applications of photons (through laser at an appropriate dose) modulates the nervous system through an integrated mechanism. This stimulated mechanism involves protein-to-protein interaction, where two or more proteins bind together to facilitate molecular processes, including modification of proteins by members of SUMO (small ubiquitin-related modifier proteins) and also protein phosphorylation and tyrosination. SUMO has been shown to have a role in multiple nuclear and perinuclear targets, including ion channels, and in the maintenance of telomeres and the post-translational modification of genes. The consequence of laser application in treatment, therefore, can be seen as influencing the transmission of neural information via an integrated and rapid modulation of ion channels, achieved through both direct action on photo-acceptors (such as cytochrome *c*-oxidase) and through indirect modulation via enzymes, including tyrosine hydroxylase (TH), tyrosine kinases and tyrosine kinase receptors. This exogenous action then facilitates an existing photonic biomodulation mechanism within the body, and initiates ion channel modulation both in the periphery and the central nervous system (CNS). Evidence indicates that the ion channel modulation functions predominately through the potassium channels, including two pore leak channels (K2P), which act as signal integrators from the periphery to the cortex. Photonic action also transforms SUMOylation processes at the cell membrane, nucleus and telomeres via signalling processes from the mitochondria (which is the main target of laser absorption) to these targets. Under the hypothesis, these observed biological effects would play a part in the bystander effect, the abscopal effect, and other systemic effects observed with the application of low level laser (LLLT). The implications of the hypothesis are important in that they point to mechanisms that can account for the effectiveness of laser in the treatment and prevention of inflammatory diseases, chronic pain and neurodegenerative disorders.

Introduction

An understanding of the nervous system and its therapeutic and endogenous modulation through laser application is important in accounting for both treatment effects and the reasons for non-responsiveness to existing treatment [1]. A research-supported explanatory account of the effect of LLLT that encompasses the diverse reported effects of laser and which provides an understanding of its treatment mechanism has become a prerequisite for the continued use of this modality in clinical practice.

Mechanisms of laser action that have been investigated to date include: mitochondrial membrane and transport modulation, neural transmission effects on the sensory neurons, motor neurons, interneurons and central nervous system [2–6] and systemic effects from signalling molecules affecting nuclear factor Kappa (NF-κB) [7], tyrosine kinases [8,9] nitrous oxide (NO) [10], reactive oxygen species (ROS) [11], peroxisome proliferator-activated receptor γ (PPARγ) [12], alpha-melanocyte-stimulating hormone

* Corresponding author. Address: Faculty of Health Sciences, 75 East St., Lidcombe, NSW 2141, Australia. Tel.: +61 293519275; fax: +61 293519278.
E-mail address: Roger.Adams@sydney.edu.au (R.D. Adams).

http://dx.doi.org/10.1016/j.mehy.2013.12.009
0306-9877/

(αMSH) [13] and other transcription factors affecting gene expression. However, an integrative mechanism that might link these neural and genetic effects remains poorly understood.

The hypothesis proposed here incorporates the established effects of laser treatment and postulates an underlying integrative mechanism for these observed effects that involves the conformational change of proteins (including ion channels) through SUMOylation (the term for protein and post-translational modification of small ubiquitin-like modifier proteins) [14] and other protein-to-protein transfer of information. SUMOylation can be seen as a broad mechanism that maintains or changes protein (or protein complex) conformation, and so alters their responses to a variety of signals [15,16]. The factors that drive SUMOylation in cells are unknown [17] but one rationale is that they require ATP and therefore the stability of a protein complex is energy-dependent [15]. The conformational energy of photons is potentially one such energy source. Therefore the rapid response of ion channels via SUMOylation and the role of SUMOylation in regulating transcription factors in the nucleus suggest that the SUMO pathway may serve to couple both acute and long term responses to environmental change [17].

The ability of organisms to respond to changing conditions over the immediate to long term requires an integrated mechanism. Action by the nervous system peripherally and centrally results in the responsiveness of the body to external stimuli. The concept of the nervous system as an integrated system has been proposed previously in theories such as the somatosensory integration theory [17], "unified theory of the nervous system" [18], Gate Theory [19], acupuncture theory and hormesis [20].

Important to the hypothesis presented here is the notion that mitochondrial metabolism processes are involved in both laser treatment effects and are themselves a source of endogenous photons [21,22]. Mitochondrial metabolism, especially the metabolic immune response of phagocytosis (cell destruction and renewal), involves metabolic release of reactive oxygen species and the resultant release of infrared light (heat). The metabolic processes that generate body heat are also processes that release photons – endogenous photons, or biophotons – in the visible light spectrum up to near infrared range of 400–820 nm [21–23]. The conformational change induced in molecules by photons is sufficient to induce conformational mobility of these molecules, disrupt active and passive transport of substances across membranes, and cause changes in membrane stability [24]. This conformational energy is proposed to be sufficient to also induce conformational change in intrinsically unstructured proteins (IUP) [25] especially prion proteins (PrPc) that are important for neural scaffolding and transport of proteins in neurons. Prion proteins are important in cellular signalling and the pathogenesis of diseases such as Alzheimer's and Ataxia [26]. Furthermore the extreme sensitivity of neural membranes and ion channels to deformation forces makes this knowledge important in the mechanobiology of brain function [27]. Even nanoscopic changes in plasma membrane deformation can influence ion channel activity [27]. In summary, consideration of the common mechanisms underlying the effects of biophotonic and LLLT conformational energy assists in the understanding of the role of biophotons in cellular signalling [23].

An understanding of the laser treatment response involves consideration of the organism's response to stimuli, including the role of mitochondria in cellular signalling [28]. Chronic pain and inflammation can be considered as immune responses [29,30], involving immune cells and glial cells [31,32]. Logically then, chronic pain and chronic inflammatory disease could also be considered to be a dysregulation of the immune response. The immune and nervous responses share the same signalling molecules, which are bidirectional and are related in embryological development to the function and regulation of the melanocyte [33], and in transcriptional regulation of the adult neural crest cells [34]. These cells include melanocytes, ocular structures, autonomic and sensory neurons and endocrine and glial cells [34]. This constitutes the linking mechanism between neural impulse and metabolism. It follows, therefore, that there may be a common shared mechanism that integrates these two pathways and that they have a combined role in mediating laser treatment effects.

An adequate explanatory account of laser treatment effects on pain and inflammation requires consideration of these known integrative signalling pathways in the neural and immune systems, which also involve the energy source of mitochondrial metabolism. Various researchers have postulated that mitochondrial-produced endogenous photons and various proteins, including ion channels (which are also proteins) may be involved in cellular communication [21,35–37]. Thar and Kuhl [35] found that certain specific cellular substrates produce chemiluminescence as a result of metabolism. It is also of note that mitochondria could be categorized as a subspecies of bacteria [38] as a consequence of their evolutionary symbiosis within the eukaryotic cell. Bacteria and other organisms demonstrate bioluminescence as a form of communication [39] in addition to chemical signalling (quorum sensing). Genes that encode these photoreceptors are highly conserved in non-phototrophic bacteria [40]. The generation of biophotons has been noted in a number of microbial systems, including bacteria, yeast and protozoa [40], and hamster cells, which have demonstrated photonic communication in a darkened room when separated by a glass window [41]. Photons have also been shown to exhibit a role in intercellular interactions in neutrophils (neutrophil bursts) [23]. These photons are emitted in wavelengths between 400 and 750 nm, the range detected by the photoreceptors of phototrophic bacteria and potentially therefore by mitochondria. In the eye, endogenously generated photons are involved in the relaying of visual information to the cortex via delayed bioluminescence [42]. Together, these observed effects demonstrate the potential for a wider existence of photonic communication.

From research on the effects of external application of photons (including laser), evidence is accumulating that photons may have a role in the mechanism of cellular communication. Sun et al. [43] have demonstrated that light, when applied to sensory and motor nerves in the periphery, can induce endogenously-generated photons in the spinal cord. They also demonstrated that different wavelengths affect the two types of nerves differently. Further, they postulate that this is a protein-to-protein transfer of information. Recently, laser at 473 nm has been shown to initiate the change in hippocampal memory formation to create a false memory in rats using optogenetics, modulating gene transcription factors (C-fos) [44]. A more general example of the influence of light is the external application of light (flashes) affecting the theta wave coherence in migraine-with-aura sufferers in a different way (photophobia) to non-sufferers of migraine. Non-sufferers have more resilience to light [45], an effect likely due to the fact that some migraine-with-aura sufferers have been shown to possess a polymorphism in potassium leak channels (TRESK mutations) [46] a finding that emphasises the importance of the link between potassium leak channels (K2P) and light as a potential neural integrator.

Consideration of neuronal homeostasis, and the mechanisms (metabolic, genetic, immune) which regulate it in an integrative way at the molecular, tissue and organism level, is of importance to health, disease and the ways in which treatment interventions either succeed or fail. These processes are important in understanding treatment effects and in formulating novel treatments, which is a primary concern of health practitioners and researchers and forms the rationale for the development of the current hypothesis.

Development of the hypothesis rationale

The hypothesis outlined here arose as a result of research into the most appropriate dose of low level laser for effective use with patients having different levels of skin pigmentation [47]. In laser treatment, a biphasic dose–response function is noted, where a minimal dose is necessary for effective treatment and an excess dose is ineffectual [4,5], so the finding that more pigmented skin absorbs more laser enabled the generation of an equation for dose adjustment [30,32].

During this research, the existence of melanin in the nervous system including the cortex [48] and sympathetic nervous system [49] was noted. This proved to be the entry point to the complex, interlinked system that could mediate the action of laser. Subsequently, a number of studies have implicated neuromelanin in neural communication and homeostasis. Melanin has a role as an organic semiconductor electrical switch involved in ion-to-electron transduction [50,51], in the transmission and modulation of nerve impulses [52] and in neuroprotection against oxidative damage in aging and Parkinson's disease [53]. It is also hypothesised to have a role in energy conservation in long distance flight of birds [54] and in epigenetic inheritance [40].

The ubiquity of melanin thus became the key entry point because melanin and its precursor molecules, including neurohormones and related enzymes tyrosine hydroxylase and tyrosine kinase, are major chromophores. It was their presence in the nervous system and sympathetic nervous system that suggested that melanin has a role in the photomodulation of neuronal input. Park [55] reviewed the role of melanocytes in the nervous system. Melanocytes and neural cells share a common embryological origin. These also share the same signalling molecules, receptors and signalling pathways and include neurotrophins, endothelins, the signalling pathways of Pro-opiomelanocortin (POMC) and the proteins p53 and p73. These pathways influence pain mediation (B opioid and αMSH), inflammation regulation (αMSH), respiratory and diurnal rhythm (melatonin) and hormones such as thyroid and sex hormones [56]. Polymorphisms in melanocortin genes result in albinism, vision and hearing impairment and variation in pain thresholds in red-headed women [57]. One of the main signalling pathways in the melanocortin system is αMSH, which is modulated by LLLT [13]. Melanocortin receptors and signalling molecules regulate inflammation, cardiovascular function and energy metabolism [56] and polymorphisms in their genes result in several diseases, including autoimmune disease [58] and idiopathic pain disorders [59].

In the initial formulation of this hypothesis, the eye was considered as a model for photon-mediated information processing, since the eye contains melanin, photoacceptors and neural circuitry – all of which are modulated by photons [60]. The adult retina is highly plastic and the neural modulation is predominantly linked through trans-membrane signalling systems. Under pathological conditions, the retina displays structural remodelling, rewiring and reprogramming. These transduction networks converge on a variety of intracellular proteins, for example, kinases, which exert subtle control over target receptors and ion channels [60]. The effect of light on this retinal neural circuitry, and its regulation via tyrosine hydrolysation, suggests a viable model for light/melanin interaction in the nervous system, due the similarities in origin, signalling pathways and the plasticity of both.

Photonic modulation of the nervous system hypothesis

The present hypothesised integrative mechanism for laser treatment effects involves protein-to-protein transfer in the neural system, especially ion channels and prion scaffolding structures, melanocortin and neurotrophin signalling and the gene and telomere system regulation. The common thread in the processes of photon modulation is the use of conformational energy to effect protein-to-protein transfer of information, which especially involves the SUMOylation of ion channels and prion proteins, and is possible due to an endogenous mechanism of photonic modulation.

The further hypothesis presented here is that these laser treatment effects are possible because this existing biological mechanism of photo-modulation involves cellular signalling. Endogenous photons are the result of the oxidation process in metabolism, which produces photons in the 450–750 nm wavelengths as a by-product of reactive oxygen species, super-oxide and nitrous oxide (NO) production. This is the wavelength range of effective LLLT.

Thus it can be hypothesised that endogenous photons act as a signalling mechanism for the regulation of neural pathways from the periphery to the cortex in an integrative manner, to help coordinate the organism's response to external and internal stimuli. There is a primary role for SUMOylation of neural pathways, genes and telomeres in this mechanism of protein-to-protein transfer that underpins photon modulation, which allows for the coordination of short term neural response to long term response of the organism to stimuli.

Fig. 1 integrates three lines of research – the effect of laser on nerves (via ion channels, calcium flux, ATP levels), on genes and telomeres (via transcription factors and increased cyclic GMP, and on the neuroimmune systems (via prion, melanocortin and neurotrophin signalling systems). All three systems demonstrate protein to protein conformational transfer by SUMOylation, phosphorylation and tyrosination.

Fig. 2 illustrates the effect that SUMOylation has on a variety of cellular processes, both as a result of LLLT and endogenous photons.

Support for the hypothesis

Research for more than forty years in Low level laser therapy (LLLT) (photon wavelength 450–910 nm) has shown that it is an effective treatment for chronic pain, wound healing, tendon muscle and nerve injury [4] especially in conditions that have previously proved unresponsive to other treatments [61]. The current conceptualisation of the mechanisms of action of LLLT involves the absorption of laser by mitochondrial photoreceptors within the mitochondrial membrane, including cytochrome-*c*-oxidase, flavins and porphoryns [4,61], conformational changes in enzymes, including Na–K ATPase and the subsequent production of ATP and an increase in nitrogen oxide (NO) production, which in turn regulates signal transduction in nerves and the cerebral cortex [61]. Laser effects have been shown to depend on the oxidative (Redox) status of the cell [28], methylation status [62] and melatonin level [63].

The following research evidence is critical to the argument.

Evidence for modulation by laser comes first from the modulation of ion channels. This includes modulation of potassium voltage and leak channels [24,64], TRPC channels [4] ATP gated channels [4,65] and calcium channels modulated by calcium flux [2,4]. Modulation is observed to occur in the peripheral nerves [2] and in the central nervous system [6]. One of these mechanisms would necessitate a SUMOylation of the Two Pore Potassium leak channels (K2P), which act as signal integrators [17].

Secondly, there is strong evidence for conformational change to signalling tyrosine kinases (including Src and Syk [66], MAPK [9] c-Met [67], c-Kit [9] and their receptors [66], which would in turn switch on or off the downstream signalling pathways. The tyrosine kinase c-Kit is also involved in the auto-phosphorylation of proteins and intracellular transduction signals [55]. These kinases

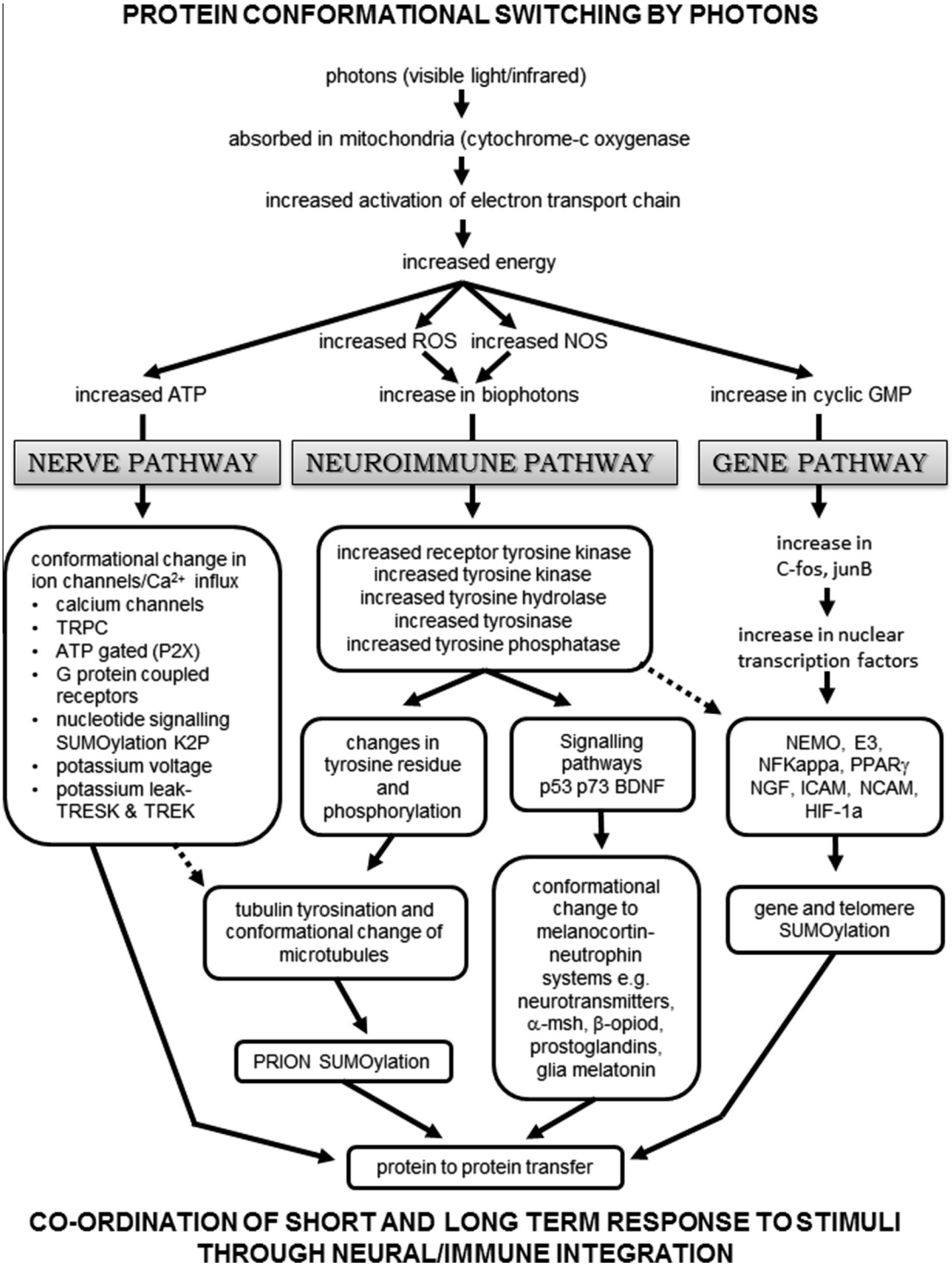

Fig. 1. Flow diagram of the mechanisms involved in protein conformational switching by photons. The figure integrates three lines of research – the effect of laser on nerves (via ion channels), on genes and telomeres, and on the neuroimmune systems (prion, melanocortin and neurotrophin signalling systems).

are in turn involved in signalling of the melanocortin and neurotrophin systems via neurotransmitters and other signalling molecules, including α-MSH, prostaglandins, glia, antiapoptotic protein Bcl-2 [28,68] and melatonin [4,13]. Hamblin and Demidova-Rice [10] have stressed the importance in the signalling cascades of cyclic adenosine monophosphate (cAMP) and nuclear factor kappa B as signal transduction pathways increasing cell proliferation and migration of fibroblasts, modulation of cytokines and inflammatory mediators. They feel that low level laser photo-disassociates NO from cytochrome *c* oxidase with the resultant increase in ATP production [10]. Modulation of the cytochrome c oxidase within the mitochondria by near infra-red light has also been inferred to act as a molecular switch [5].

Conformational change to microtubules is involved in the trafficking of proteins and mitochondria in the nervous system [69]. Karu [70] used visible and near-infrared laser to activate retrograde trafficking of transduction signals from the mitochondria to the cell membrane. Tubulin proteins, as well as being affected by SUMOylation (K2P channel TREK as ligand), are tyrosinated and these modifications could generate a dynamic microtubule

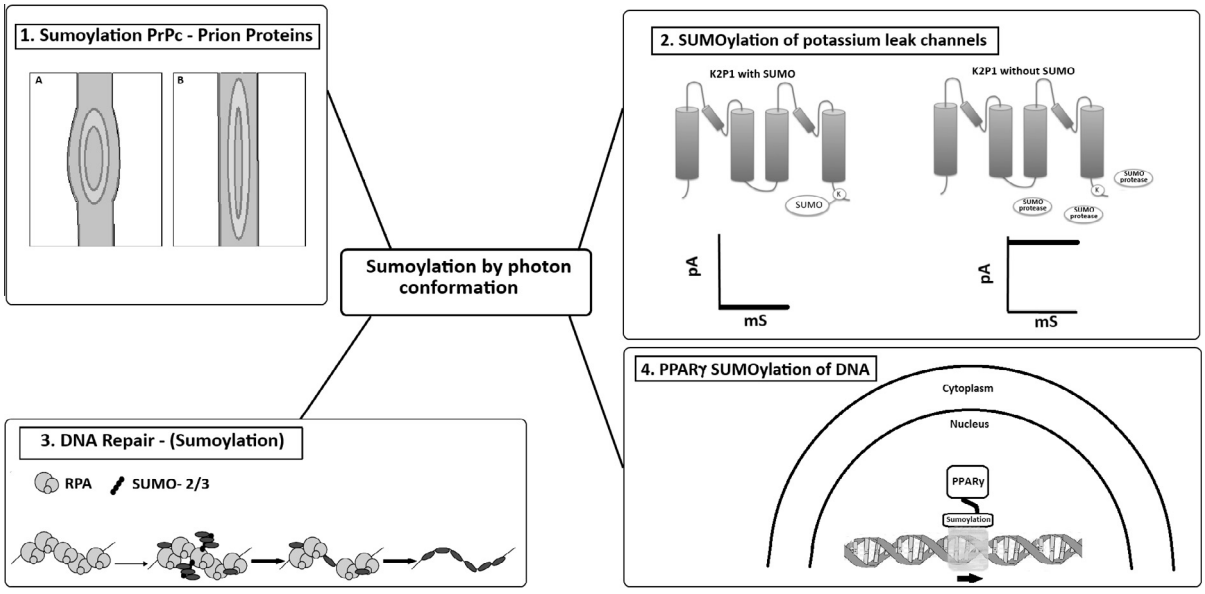

Fig. 2. Schematic diagram showing the involvement of the SUMO molecule in prion proteins, potassium channels, telomere repair and post-translational modification of genes. The three sections of the diagram show the effect of photons on SUMOylation in cells (1) sympathetic C-fibre neuron (varicosities). SUMOylation has β-tubulin as ligand for prion protein tyrosination, A after SUMOylation, B before SUMOylation (adapted from Chow [3]). (2) SUMOylation of potassium leak channel K2P1, showing an all or nothing response. pA = picoamperes, mS = milliseconds (adapted from Plant [17]). (3) Representation of SUMOylation in DNA repair response, adapted from Dou et al. [72]. RPA = replication protein A, (4) Representation of the effect of LLLT on SUMOylation and subsequent repression of inflammatory genes via PPARγ [12].

coding system in the neuronal cytoskeleton [71]. Evidence for β-tubulin modification has been provided by Chow et al. [3] when they noted that varicosities were created in cultured dorsal root ganglia neurons (80% of which were nociceptors). This occurred following a laser irradiation dose that was equivalent to a lignocaine nerve block. The modulation of β-tubulin is now hypothesised to result in the SUMOylation of prion proteins.

The increase in ROS, NO and subsequent change in the availability of cyclic GMP affects nuclear transcription factors and nuclear transport proteins. This results in the SUMOylation of genes, most particularly the transrepression of inflammatory genes. An example is the C3 inflammatory gene [73] in macular degeneration treatment and prevention [74]. It is noted in these studies that there is an abscopal effect, whereby not only the irradiated eye is improved, but also the non-irradiated eye. An abscopal effect is defined as a reaction of cells within an organism that have not been directly exposed to irradiation and is assumed to be mediated by the immune system via cytokines [75]. The mechanism is also evident in laser abscopal effects in the heart [76], in tooth movement [77] and most recently, in the prevention of Parkinson's disease in an animal model where there was a neuroprotective effect via prevention of TH in the brains of irradiated guinea pigs, when laser was applied to the shoulders or hips. Although laser at both sites was effective, irradiation at the closer shoulder was more effective [78]. A further example is the inflammatory genes involved in post-operative effusion by the increase in the anti-inflammatory transcription factor PPARγ [12]. SUMOylation and PPAR are interdependent in the transrepression of the inflammatory response [79] Antioxidant genes (MnSOD) are also up-regulated [6] as are DNA repair genes [80].

The role of laser effects and endogenous photons on gene transcription should be analysed in parallel [23] and Fig. 1 demonstrates how the three major signalling systems in the body can be integrated to encompass short term response of the organism through rapid neural response, through to medium and long term response, operating via neurotrophin, melanocortin and gene modulation processes.

Conclusion

Current research findings underpin the hypothesis that laser treatment effects – which are known to be complex, varied and nuanced – are the result of an integrated mechanism involving the conformational energy of photon-acting modulating protein-to-protein transfer, primarily through SUMOylation. This is possible because of the presence of an underlying biophoton emission mechanism, occurring as a result of redox status ROS induced emission at the submitochondrial level and retrograde signalling between the mitochondria nucleus and cell membrane. SUMOylation can be modulated by photon conformational energy and involves the regulation of ion channels, prion proteins, telomeres and the cell nucleus. Many diseases that involve the dysregulation of inflammation, cell transduction signalling and prion diseases are known to be modulated by laser. The hypothesis outlined here provides a basis for understanding and integrating existing evidence from research trials on laser treatment for diseases that have included unresponsive pain, neurodegenerative diseases and inflammatory diseases, arthritis and macular degeneration.

Conflict of interest

None of the authors of 'Protein conformational modulation by photons: a mechanism for laser treatment effects' have any financial or personal relationships with people or organizations that could inappropriately influence our work.

There were no sources of funding or sponsors for this work, for any part of the research and writing of the manuscript.

References

[1] Liebert A, Rebbeck T, Elias S, Hawkins D, Adams R. Musculoskeletal physiotherapists' perception of non-responsiveness to treatment for cervicogenic headache. Physiother Theory Pract 2013;29:616–29.
[2] Chow R, David M, Armati P. Inhibitory effects of laser irradiation on peripheral mammalian nerves and relevance to analgesic effects: a systematic review. Photomed Laser Surg 2011;29:365–81.

[3] Chow R, David M, Armati P. 830 nm laser irradiation induces varicosity formation, reduces mitochondrial membrane potential and blocks fast axonal flow in small and medium diameter rat dorsal root dorsal root ganglion: implications for the analgesic effects of 830 nm laser. J Peripher Nerv Syst 2007;12:28–39.
[4] Huang Y-Y, Chen A-H, Carroll J, Hamblin M. Biphasic dose response in low level light therapy. Dose–Response 2009;7:358–83.
[5] Moro C, el Massri N, Torres N, Ratel D, de Jaeger X, Chabrol C, et al. Photobiomodulation inside the brain: a novel method of applying near-infrared light intracranially and its impact on dopaminergic cell survival in MPTP-treated mice. J Neurosurg 2013. http://dx.doi.org/10.3171/2013.9.JNS13423.
[6] Naeser MA, Saltmarche A, Krengel MH, Hamblin MR, Knight JA. Improved cognitive function after transcranial light-emitting diode treatments in chronic, traumatic brain injury: two case reports. Photomed Laser Surg 2011;29:351–8.
[7] Chen A. Low-level laser therapy activates NF-κB via generation of reactive oxygen species in mouse embryonic fibroblasts. PLoS One 2011;6:1–8.
[8] Song S, Zhou F, Chen W. Low-level laser therapy regulates microglial function through Src-mediated signaling pathways: implications for neurodegenerative diseases. J Neuroinflammation 2012;9:219–38.
[9] Wu S, Xing D. Intracellular signaling cascades following light irradiation. Laser Photonic Rev 2013:1–16.
[10] Hamblin M, Demidova-Rice T. Cellular chromophores and signaling in low level light therapy. Prog Biomed Opt Imaging 2007;6428 [article 6428-02].
[11] Lavi R, Shainberg A, Shneyvays V, Hochauser E, Isaac A, Zinman T, et al. Detailed analysis of reactive oxygen species induced by visible light in various cell types. Lasers Surg Med 2010;42:473–80.
[12] de Lima FM, Albertini R, Maia-Filho AL, Santana CdeL, Castro-Faria-Neto HC, Franca C. Low-level laser therapy restores the oxidative stress balance in acute lung injury induced by gut ischemia and reperfusion. Photochem Photobiol 2013;89:179–88.
[13] Laakso L, Gramond T, Richardson C, Galligan JP. Plasma Acth and β-endorphin levels in response to low level laser therapy (LLLT) for myofascial trigger points. Laser ther 1994;6:133–42.
[14] Hay R. SUMO: a short history of modification. Mol Cell 2005;18:1–12.
[15] Seeler JS, Dejean A. Nuclear and unclear functions of SUMO. Mol Cell Biol 2003;4:690–9.
[16] Wilkson K, Nakamura Y, Henley JM. Targets and consequences of protein SUMOylation in neurons. Brain Res Rev 2010;64:195–212.
[17] Plant L. A role for K2P channels in the operation of somatosensory nociceptors. Front Mol Neurosci 2012;5:1–11.
[18] Harris S. The Unified Theory of the Nervous System and Behavior. <http://www.stevenmichaelharris.com/theory/>; 2013 [accessed 01/09/2013].
[19] Melzack R. Gate control theory, on the evolution of pain concepts. Pain Forum 1996;5:128–38.
[20] Ristow M, Zarse K. How increased oxidative stress promotes longevity and metabolic health: The concept of mitochondrial hormesis (mitohormesis). Exp Gerontol 2010;45:410–8.
[21] Salari V, Rahnama M, Tuszynski J. Dissipationless transfer of visual information from retina to the primary visual cortex in the human brain. Activitas Nervosa Superior 2012;54:26–48.
[22] Klima H. Stimulation by laser light in dissipative biological systems. In: Kert J, Rose L, editors. Clinical laser therapy: low level laser therapy. Veksoe, Denmark: P-Laser Systems International; 1989. p. 30–40.
[23] Tafur J, van Wijk E, van Wijk R, Mills P. Biophoton detection and low-intensity light therapy: a potential clinical partnership. Photomed Laser Surg 2010;28:23–30.
[24] Ignatov Y, Vislobokov A, Vlasov T, Kolpakova M, Mel'nikov K, Petrishchev I. Effects of helium–neon laser irradiation and local anesthetics on potassium channels in pond snail neurons. Neurosci Behav Physiol 2005;35:871–5.
[25] Das S, Mukhopadhyay D. Intrinsically unstructured proteins and neurodegenerative diseases: conformational promiscuity at its best. IUBMB Life 2011;63:478–88.
[26] Linden R, Martins V, Prado M, Cammarota M, Izquierdo I, Brentani R. Pysiology of the prion protein. Physiol Rev 2008;88:673–728.
[27] Tyler W. The mechanobiology of brain function. Nat Rev Neurosci 2012;13:867–78.
[28] Bisland S, Wilson B. To begin at the beginning: the science of bio-stimulation in cells and tissues. In: Hamblin M, Waynant R, Anders J, editors Mechanisms for low-light therapy; 2006. http://dx.doi.org/10.1117/12.647675.
[29] Watkins L, Maier S. Neuropathic pain: the immune connection. Pain Clin Updat 2004;12:1–4.
[30] Szentivanyi A, Berczi I, Nyanteh H, Goldman A. Some evolutionary, morphoregulatory and functional aspects of the immune-neuroendocrine circuitry. Neuroimmune Biol 2003:31–61.
[31] Thacker M, Clark A, Bishop T, Grist J, Yip PK, Moon LD. CCL2 is a key mediator of microglia activation in neuropathic pain states. Eur J Pain 2009;3:263–72.
[32] Thacker M, Clark A, Marchand F, McMahon S. Pathophysiology of peripheral neuropathic pain: immune cells and molecules. Anaesth Analg 2007;105:838–47.
[33] Yaar M, Park H. Melanocytes: a window into the nervous system. J Invest Dermatol 2012;132:835–44.
[34] Hou L, Pavan W. Transcriptional and signaling regulation in neural crest stem cell-derived melanocyte development: do all roads lead to Mitf? Cell Res 2008;18:1163–76.
[35] Thar R, Kühl M. Propagation of electromagnetic radiation in mitochondria? J Theor Biol 2004;230:261–70.
[36] Traill R. Meaningful UV and IR photon-exchange within bio-tissue? – interdisciplinary evidence, and a new way to view asbestos toxicity. Gen Sci J 2010;14:1–20.
[37] Bernroider G, Roy S. Quantum entanglement of K+ ions: Multiple channel states and the role of noise in the brain. Int Soc Opt Eng (SPIE) 2005;5841 [paper 5841–29].
[38] Pallen MJ. Time to recognise that mitochondria are bacteria? Trends Microbiol 2011;19:58–75.
[39] Zan J, Cicirelli EM, Mohamed NM, Sibhatu H, Kroll S, Choi O, et al. A complex LuxR–LuxI type quorum sensing network in a roseobacterial marine sponge symbiont activates flagellar motility and inhibits biofilm formation. Mol Microbiol 2012;85:916–33.
[40] Reguera G. When microbial conversations get physical. Trends Microbiol 2011;19:105–13.
[41] Albrecht-Buehler G. Autofluorescence of live purple bacteria in the near infrared. Exp Cell Res 1997;236:43–50.
[42] Wang C, Bokkon I, Dai J, Antal I. Spontaneous and visible light-induced ultraweak photon emission from rat eyes. Brain Res 2011;1369:1–9.
[43] Sun Y, Wang C, Dai J. Biophotons as neural communication signals demonstrated by in situ biophoton autography. Photochem Photobiol Sci 2010;9:315–22.
[44] Ramirez S, Liu X, Lin P-A, Suh J, Pignatelli M, Redondo RL, et al. Creating a false memory in the hippocampus. Science 2013;341:387–91.
[45] Mendonca-de-Souza M, Monteiro UM, Bezerra AS, Silva-de-Oliveira AP, Ventura-da-Silva BR, Barbosa MS, et al. Resilience in migraine brains: decrease of coherence after photonic stimulation. Front Hum Neurosci 2012;6:1.
[46] Laffreniere R, Cader Z, Poulin J, Andres-Enguix I, Simoneau M, Gupta N, et al. A dominant-negative mutation in the TRESK potassium channel is linked to familial migraine with aura. Nat Med 2010;16:1157–61.
[47] Liebert A, Waddington G, Bicknell B, Chow RT, Adams R. Quantificatioin of the absorption of low-level 904 nm super pulsed light as a function of skin colour. In: Laakso E-L, Young C, editors. 9th WALT congress. Gold Coast, Australia: Medimond; 2012. p. 11–5.
[48] Zecca L, Zucca F, Wilms H, Sulzer D. Neuromelanin of the substantia nigra: a neuronal black hole with protective and toxic characteristics. Trends Neurosci 2003;26:578–80.
[49] Fu Y, Kaye G, Lattes R. Primary malignant melanocytic tumors of the sympathetic ganglia with an ultrastructural study of one. Cancer 1975;36:2029–41.
[50] Mostert AB, Powell BJ, Pratt FL, Hanson GR, Sarna T, Gentle IR, et al. Role of semiconductivity and ion transport in the electrical conduction of melanin. Proc Nat Acad Sci 2012;23:8943–9.
[51] McGinness J, Correy P, Proctor P. Amorphous semiconductor switching in melanins. Science 1974;183:853–5.
[52] Nicolaus B. A critical review of the function of neuromelanin and an attempt to provide a unified theory. Med Hypotheses 2005;65:791–6.
[53] Zecca L, Casella L, Albertini A, Sulzer D. Neuromelanin can protect against iron-mediated oxidative damage in system modeling iron overload of brain aging and Parkinson's disease. J Neurochem 2008;106:1866–75.
[54] Goodman G, Bercovich D. Melanin directly converts light for vertebrate metabolic use: heuristic thoughts on birds, Icarus and dark human skin. Med Hypothesis 2008;71:190–202.
[55] Yaar M, Park H-Y. Melanocytes: a window into the nervous system. J Invest Dermatol 2012;132:835–44.
[56] Adan R, Gispen W. Melanocortins and the brain: from effects via receptors to drug targets. Eur J Pharmacol 2000;405:13–24.
[57] Mogil JS, Ritchie J, Smith SB, Strasburg K, Kaplan L, Wallace MR, et al. Melanocortin-1 receptor gene variants affect pain and μ-opioid analgesia in mice and humans. J Med Genet 2005;42:583–7.
[58] Tsantikos E. Dissecting autoimmune disease susceptibility in Lyn-deficient mice. Medicine, Dentistry and Health Science vol. PhD, University of Melbourne; 2011.
[59] Diatchenko L, Nackley A, Slade G, Fillingim R, Maixner W. Idiopathic pain disorders – pathways of vulnerability. Pain 2006;123:226–30.
[60] R. Marc, Functional neuroanatomy of the retina. <http://prometheus.med.utah.edu/~marclab/mss/duanes2/Marc_Duanes_FNAR_20080815.pdf>; 2009.
[61] Chow RT, Johnson MI, Lopes-Martins RAB, Bjordal JM. Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomised placebo or active-treatment controlled trials. Lancet 2009;374:1897–908.
[62] Abrahamse H, Vorster L, Houreld N. Global DNA methylation status of colorectal cancer cells exposed to photodynamic therapy. In: Laasko L, Young C, editors. 9th WALT congress. Gold Coast, Australia: Medimond; 2013. p. 1–4.
[63] Karu T, Pyatibrat L, Ryabykh T. Melatonin modulates the action of near infrared radiation on cell adhesion. J Pineal Res 2003;34:167–72.
[64] Karu T, Kurchikov A, Letokhov V, Mokh V. He–Ne laser radiation influences single-channel ionic currents through cell membranes: a patch-clamp study.

In: Proc. SPIE 3198, Effects of low-power light on biological systems; 1997. http://dx.doi.org/10.1117/12.298001.
[65] Karu TI, Pyatibrat LV, Kalando GS. Cell attachment to extracellular matrices is modulated by pulsed radiation at 820 nm and chemical that modify the activity of enzymes in the plasma membrane. Lasers Surg Med 2001;29:274–81.
[66] Song S, Zhou F, Chen W. Low-level laser therapy regulates microglial function through Src-mediated signalling pathways: implications for neurogenerative diseases. J Neuroinflammation 2012;9:219–25.
[67] Gao X, Xing D. Molecular mechanisms of cell proliferation induced by low power laser irradiation. J Biomed Sci 2009;16:1–16.
[68] Zhang H, Xing D, Wu S, Sun X. Protein kinase C promotes cell apoptosis induced by high fluence low-power laser irradiation. In: Proc. SPIE 7519, Eighth international conference on photonics and imaging in biology and medicine; 2009. http://dx.doi.org/10.1117/12.841566.
[69] Martins V, Beraldo F, Hajj G, Lopes MH, Lee KS, Prado MAM, et al. Prion-protein: orchestrating neutrotrophic activties. Curr Issues Mol Biol 2010;12:63–86.
[70] Karu T. Mitochondrial signaling in mammalian cells activated by red and near-IR radiation. Photochem Photobiol 2008;28:1091–9.
[71] Janke C, Kneussel M. Tubulin post-transformational modifications: encoding functions on the neuronal microtubule cytoskeleton. Trends Neurosci 2010;33:362–72.
[72] Dou H, Huang C, Nguyen TV, Lu L-S, Yeh ETH. SUMOylation and de-SUMOylation in response to DNA damage. FEBS Lett 2011;585:2891–6.
[73] Rutar M, Natoli R, Albarracin R, Valter K, Provis J. 670-nm light treatment reduces complement propagation following retinal degeneration. J Neuroinflammation 2012;9:1–10.
[74] Guymer R, Brassington K, Dimitrov P, Vingrys AJ, Plunket, MJ. Novel nanosecond laser treatment to prevent vision loss from age-related macular degeneration. Paper from 4th Annual Scientific Congress at RANZCO; 2010.
[75] Schmid T, Multhoff G. Non-targeted effects of photon and particle irradiation and the interaction with the immune system. Front Oncol 2012;2:1–4.
[76] Oron U, Yaakobi T, Oron A, Mordechovitz D, Shofti R, Hayam G, et al. Low-energy laser irradiation reduces formation of scar tissue after myocardial infarction in rats and dogs. Circulation 2001;103:296–301.
[77] Fujita S, Yamaguchi M, Utunomiya T, Yamamoto H, Kasai K. Low-energy laser stimulates tooth movement velocity via expression of RANK and RANKL. Ortho Craniofac Res 2008;11:143–55.
[78] Shaw V, Spana S, Ashkan K, Stone J, Baker GE, Mitrofanis J. Neuroprotection of midbrain dopaminergic cells in MPTP-treated mice after near-infrared light treatment. J Comp Neurol 2010;518:25–40.
[79] Pascual G, Fong A, Ogawa S, Gamliel A, Li AC, Perissi V, et al. A SUMOylation-dependent pathway mediates transpression of inflammatory response genes by PPAR-y. Nature 2005;437:759–63.
[80] da Fonseca A, Mencalha A, de Campos V, Machado SCM, Peregrino AA, Geller M, et al. DNA repair gene expression in biological tissues exposed to low-intensity infrared laser. Lasers Med Sci 2013;28:1077–84.