The Role Of Channelopathies In Pain And The Implications For Laser Treatment

Liebert A.[1], Bicknell B.[2]

1 University of Sydney, Sydney, Australia
2 Australian Catholic University, Sydney, Australia
artarmonphysio@bigpond.com

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1 Introduction

People affected by chronic pain conditions suffer the additional burden of loss of income and negative impact on daily life activities. Chronic pain patients are often unresponsive to currently available therapies and may benefit from a novel approach to treatment. For example, in cervicogenic headache 25% of patients are unresponsive to physiotherapy treatment [1]. Some chronic pain conditions can be viewed as channelopathies. Channelopathies are acquired or genetic dysfunctions of the sodium or potassium ion channels that underpin the nervous transmission, and several common pain conditions have been recently found to have channelopathies as either primary pathogenesis or as comorbidity, e.g. Headache including Migraine with Aura [2], Familial Hemiplegic Migraine Type I + II (calcium and sodium channelopathies)[3], Polymodal Pain Disorders (potassium channelopathy)[4] Irritable Bowel Syndrome and Erythermalgia (sodium channelopathy)[3].

These conditions often have poor clinical outcomes with current management. However an exogenous agent could potentially modulate the pathophysiology of channelopathy. Therapeutic laser is one such agent. The implications of current research into modulation of sensorimotor and second and third order neurons and its relevance to channelopathic pain are discussed here. We review the mechanisms of laser modulation of nerve excitability [5], neuroendocrine effects [6] and central nervous systems modulation via signalling pathways in the CNS [7]. An understanding of pain channelopathies and their relevance to pain pathways is important for those involved in the treatment of chronic pain. Acquired ion channel dysfunction has also been linked to chronic pain evoked by physical insults. Accordingly, current research in humans and transgenic animals is reviewed here, with particular reference to 1) the role of potassium channels in the modulation of the somatosensory pain system and 2) the known and postulated mechanisms whereby laser can affect this system in channelopathies.

2 Aim

The purpose of this paper is to review recent basic research into the role of nerve channelopathies in chronic pain syndromes, because research over the past few years has pointed to a significant role of neuronal channelopathies in the genesis of chronic pain. Both the general public and researchers are fascinated by disease and detective stories, and channelopathy research is both of these [8].

Channelopathies exist in all neuronal channels in the body, however this paper will concentrate on the channelopathies encountered in patients who are unresponsive to treatment, and seen in primary care centres. The paper also considers previously researched and postulated mechanisms by which laser can modulate pain arising from impaired nerve channels.

3 Channelopathies

Common pain conditions - including chronic neck pain, chronic non-specific back pain, cervicogenic headache, migraine, temperomandibular joint (TMJ) dysfunction, radicular pain, painful arthritis, neuralgia, fibromyalgia and pain associated with hypermobility syndromes - account for a large portion of patients attending pain clinicians, neurologists, physiotherapists, general practitioners and other alternative health professionals. These conditions represent a considerable burden in terms of the associated loss of income and loss of ability to perform activities of daily living.

Increasingly, researchers have investigated the role of impaired ion channels in both the genesis of these conditions and as regards their comorbidity [3, 8].

Channelopathies are diseases caused by disturbed function of ion channel subunits or the proteins that regulate them. The diseases can be either congenital, resulting from a mutation or mutations to the encoding genes, or acquired, often resulting from an autoimmune attack on an ion channel. Although heritable, pain channelopathies associated with somatic mutations can occur.

Neuropathic pain may arise from misexpression of ion channels as a consequence of physical insults, viral infections or toxic drugs [9]. This misexpression of ion channels is potentially reversible, one example being glial cell derived growth factor (GDNF), which can normalize the regulation of Nav 3 expression and reverse neuropathic pain in arousal modes where neurons have been severed [10]. Kullman [11] found that small incremental compensatory actions by other ion channels can also normalize ion function. All ion channels can have the potential for dysfunction, and channelopathy can exist in various forms in peripheral ion channels, mitochondrial ion channels, skeletal muscle, smooth muscle, the spinal cord and in the cortical neurons. That is, all ion channels have the potential to become dysfunctional.

Dysfunction of ion channels within the spinal cord can result in central sensitisation of pain [9]. The mechanism for this central sensitised pain includes the action of calcium-activated potassium channels which, when impaired by pro-inflammatory mediators cause ion channel hyperexcitability and induced hyperalgesia. If the neuropeptide tyrosine is also blocked from exerting its modifying effect on threshold excitation of the potassium channel, the result is neurogenic pain [12]. Dray also concludes that some inflammatory modifications can produce manifold and complex changes in afferent fibres [12], ranging from overt activation of ion channels to the sensitization of these channels to other stimuli. Examples of these include proinflammatory kinins such as prosteanoids and cytokins. In addition, bradykinins can activate B2 kinin receptors and can be involved either directly, or indirectly through the release of prostaglandins from macrophages and leucocytes [12].

Dysregulated neural ion channels, which have increased pain threshold sensitivity, are often unresponsive to treatment and have poor clinical outcomes given current management. Chronic pain associated with genetic mutations of the potassium 2 pore leak channels (K2P) include polymodal pain syndrome (K2P2 = TREK mutation) and migraneneurs (K2P18 = TRESK) and other hypothesized TRESK polymorphism headache conditions (such as cervicogenic headache), often do not respond to opioid drugs, physiotherapy [13, 14] radiofrequency neurotomy or to surgery [15]. Acquired channel sensitivity, for example lumbar disc dorsal root ganglion (DRG) sensitivity, or neural dysfunction in ion channels in Guillain-Barre Syndrome, both contribute to neuropathic pain. This is also present in other viral arthropathies such as Ross River Fever [9]. Central sensitivity in the case of chronic fatigue pain processing is mediated through a range of dysregulated channels and cytokine cascades in the DRG and insular and cingulate cortex [16].

Genetic channelopathies are involved in the neuropathic pain in migraine with aura and familial hemiplegic migraine (FHM). It is postulated that other headache types such as cervicogenic headache (CH) may also be a (TRESK) channelopathy. Bovim [17] found similar impairment in pressure threshold sensitivity over C4 unilaterally in CH compared to bilateral impairment in migraine with aura. This feature was absent in both migraine without aura and tension type headache. Other channelopathies associated with increased pain response include hypersensitive pain syndrome, sodium channelopathy [3], irritable bowel syndrome and erythermalgia. In erythromyalgia, congenital sensitivity can be experienced early or late depending on compensatory mechanisms [3].

Hall [14] and Niere [13] have both postulated that pain arising from neural structures does not respond to conventional physiotherapy that is aimed at mechanical or muscle structures. In a recent study of physiotherapist perceptions of unresponsive cervicogenic headache [18], clinicians proposed that neural sensitivity, genetic factors, severe trauma, comorbidities and latency of response to treatment were the main determinants of non responsiveness. Recent studies report the presence of neural sensitivity in chronic neck pain and CH (7-10%)[19, 20] and non-specific chronic low back pain [21]. Hall, Briffa and Hopper [14] suggested sub-classification of neural sensitivity into three categories: 1) peripheral neural sensitization, characterized as exhibiting increased nerve trunk mechanosensitivity; 2) denervation, characterized by signs of nerve conduction deficit; and 3) central sensitization, the mechanism of which has been explained as involving modulation of pain processing centres in the brain, including the insular cortex, cingulate cortex, hypothalamus and pre-frontal cortex [22, 23]. Importantly, abnormal ion channels can be involved in all of these conditions.

3 Mechanisms of Laser Modulation of Channelopathy Pain

Once laser is absorbed [23], the question can be asked as to how laser might modulate the dysregulation of Ion channels that result from congenital and acquired channelopathy? There are several possible actions associated with the bioelectrical and biochemical effects of laser.

Firstly, laser is absorbed by mitochondrial photoreceptors within the membrane, including cytochrome-C-oxidase . This can induce conformational change in enzymes, including Na-K ATPase and the subsequent

production of ATP in mitochondria. Depending on the dose, ATP can be increased or decreased to modulate ion function. A biphasic dose response has been noted [24]. The resultant increase in mitochondrial respiration can also increase reactive oxygen species (ROS) and modulate nitrogen oxide (NO) production, which can in turn regulate signal transduction in the nerves [7, 25].

Secondly, laser can directly block the axonal transport of mitochondria and influence mitochondrial membrane potential [26]. It also blocks retrograde flow of depleted mitochondria so that they are unable to produce ATP. This is accomplished by a change in neuronal architecture, varicosity formation, mitochondrial clustering and microtubule disarray that results in conduction block [27]. In this work, Chow also noted that 830 nm laser exerts pain-relieving effects via the PNS with nociceptive specific inhibition, and further proposed that absorption of laser energy and its transduction into electrochemical and/or electro-physical events triggers a secondary cascade of cell specific events, a sequence that has also been suggested by Karu and colleagues [28].

Thirdly, laser can affect neuro-endocrine modulation. Shimoyama [6] found that LLLT depresses sympathetic ganglionic transmission due to the hyperpolarisation of ganglionic cells, as part of its mechanism of action. In this work, there was a direct effect on the neurotransmitter release or its receptor uptake due to an unknown mechanism. He also noted a biphasic effect.

Fourth, laser has the potential to modulate the nervous system more broadly. Evidence for more a systemic effect of laser has been demonstrated in studies by Tuby [29] and Oron [30], where effects on areas distal to the irradiated parts have been observed. Chow [27] hypothesised that there would be a reorganisation of neurons reflecting neuroplasticity and adaptive change in the dorsal root ganglion (DRG), which produces an altered response to nociceptive input. There would be a flow-on effect by this modulation to the second order neurons, and a further modulation of the ascending and descending pain pathways.

We need to ask: why might laser be effective here, in terms of these underlying mechanisms, when other pain relieving measures (opioid drugs, physiotherapy) are not working? One possibility is the view that laser has the potential to modulate the nervous system through an integrated mechanism that operates systemically through action on photo-receptors, such as cytochrome C oxidase, and indirectly through action of enzymes such as tyrosine hydroxylase, which are present in the peripheral, spinal and central nervous system ion channels [32]. These ion channels have their ionic gradients established by Na^+ K^+ ATPase and are regulated by calcineurin and thyroid hormones. Recent research has found a role for K^+ ion channels to integrate a neural response to nociception [31]. Two pore K leak channels (K2P) have been found to be polymodal neural signal integrators, that is, they are important in responding to multiple stimuli.

3.1 Laser and the modulation of the somatosensory nociceptive and pain system in channelopathies

3.1.1 The role of K^+ channels in nociception

K2P are important in modulating neural sensitivity [31]. They act as both ion channels and receptors to sense mechanical, thermal and chemical stimuli via their terminals at nociceptive sensory nerve fibres, and they also determine nociceptor excitability and conductivity. K2P sensory receptors include: K2P ion channels, transient receptor potential channels (TRPC), acid sensory channels (ASIC), P2X receptors and voltage gated K^+, Na^+ and Ca^{2+} channels. Voltage-gated Potassium channels are regulated by ligand residues that are completely dependent on the availability of tyrosine. K2P leak channels contain a selectivity filter with tyrosine at its core.

All of these K2P channels operate through somatosensory neurons to determine excitability, synaptic function and neural responsiveness from distant sites in the body to higher processing centres of the brain [31]. Plant [31] concluded that K2P channels are important as polymodal signal integrators and respond to "neurogenic and immune inflammatory signalling pathways, feedback control of neurotransmitter release in the CNS" and are likely to regulate somatosensory neurons in both acute and chronic pain. These feedback control mechanisms may be important in neuronal homeostasis and possibly have a role in fine-tuning neural regulatory mechanisms.

3.1.2 The role of laser in modulation of K2P channels

The author proposes that low level laser can modulate K2P channels via the photonic activation of tyrosine hydroxylase and the subsequent increased production of tyrosine [32, 33] as well as its secondary modulation of the melanocortins and their receptors [34]. Tyrosine(Tyr) is formed by melanosomes during the formation of pigment cells and differentiated sympathetic neurotransmitters. Tyrosine hydroxylase is also the rate-limiting enzyme for the receptor to open the ligand gate of voltage K^+ channels. The modulation of the melanocortin pain system occurs through modulation of pro-opiomelanocortin (POMC) protein and its derivatives, adrenocorticotrophic hormone (ACTH) and alpha melanocyte stimulating hormone (αMSH). These

hormones have been found to be affected by LLLT in a study by Laakso [34] on the modulation of myofascial pain.

Many molecules incorporating Tyr are present in the K2P neural system, from the periphery to the cortex, and include neuropeptides (such as neuropeptide tyrosine (NPY)), hormones (such as α-melanocyte stimulating hormone (αMSH) , melanin concentrating hormone (MCH)), neurotransmitters (such as acetyl choline, epinephrine, norepinephrine, serotonin), melanocortin receptors (MCIR), signalling molecules (such as Tyr, TyrP1, MITF), selectivity filters (K2P selectivity filter) and ligand molecules (K voltage channels NPY).

These K2P channels are electrically silent [31] and laser may modulate their action by several mechanisms, such as

1. Direct change of membrane potential through the direct stimulation of ATPase
2. Modulating the K voltage channels including (NPY as ligand) [31, 35]
3. Transforming K2P channels by Tyr involvement in the sumoylation of the leak channel [31].
4. Changing mitochondrial fast axonal flow [27]
5. Modulating the TRPC receptors, [36, 37]
6. Modulating αMSH [34] and the Melanocortin and β opioid system, which prevents NF-KB activation [38]
7. Influencing the action of tyrosine hydroxylase [32]
8. Modulating the release of neurotransmitters containing Tyr (acetylcholine, epinephrine, norepinephrine)
9. Regulation of NPY as a signalling molecule acting on second order neurons and influencing ion channels in the brainstem, hypothalamus, insular and cingular cortex, including the release of BDNF [39]
10. Modulating the selective filtering of melanin specific receptors (Melanocortin MC3 and MC4 [38], Y1 + Y2 receptors the ligand responses to a single amino acid tyrosine) [40]

3.2 Further modulation of the somatosensory nociceptive and pain system in channelopathies

A further relevant mechanism is the potential regulation of ion channels by endogenously occurring photons [37]. The argument here is that the body cannot function fully by nerve electrical transmission alone, since this mechanism is simply not fast enough [37]. Recent research by Rahnama and colleagues has supported this idea: "synaptic transmission and axonal transfer of nerve impulses are too slow to organize co-ordinated activity in large areas of the central nervous system" [41]. Since modulation of the somatosensory system can occur with laser, it may be that an underlying endogenous photonic mechanism of self-regulation exists.

3.2.1 Critical recent research papers informing the channelopathy modulation hypothesis

A more efficient neural transmission process is proposed wherein photonic quantum transference of information is present. The first person to consider photonic neural transmission was Cope, who postulated in 1973 that mitochondrial lipid membranes acted as resonance chambers and stored an IR standing wave [27, 42]. He postulated that the storage of infrared as standing waves is possible within mitochondrial lipid membranes, and that it involves redox potential and energy transduction.

This mechanism was further developed by Albrecht-Buehler in 1992, in his conceptual outline of cellular vision. In a study using hamster kidney cells, the cells were inoculated on one side of a glass film, the opposite side of which was covered with a 2-3 day old confluent layer of BHK cells. Seven hours after attaching and spreading in the absence of visible light, most of the cells had aligned their long axes in the direction of the whorls of the confluent cells opposite. A thin metal coating on the glass films inhibited the effect. In contrast, a thin coat of silicon on the glass did not inhibit the effect, suggesting that it was caused by red or near-infrared light. Albrecht-Buehler concluded that "biophotonic signals generated by light stimulation consist of two components: action and background biophotons. A possible explanation for this observation is that external light stimulation might generate action biophotons, being able to conduct along the neural fibers, and result in an increase in biophotonic activity"[42].

The next significant evidence was provided by Thar and Kuhl, in 2004 [43], who speculated that there is long range interaction between mitochondria mediated by electromagnetic radiation. They suggested that "Chemiluminescence from mitochondria originates generally from excited molecules generated by the oxidative metabolism of mitochondria." The ability of these organelles to provide light guiding structures is made possible by the cellular network of microtubules and filamentous mitochondria. They hypothesize that the light generated internally within the mitochondria, would be "emitted at both ends of the mitochondria with high temporal coherence and high directivity i.e., mitochondria would act like lasers".

The generation of endogenous photons has been noted in a number of biological systems, including bacteria, yeast, and protozoa, which produce weak electromagnetic radiation or light from exergonic chemical reaction [29, 44]. Interestingly, it has been well known for many years that mitochondria originated in cells from

bacterial symbiotes. Populations of bacterial cultures are able to influence growth parameters of other cultures, by photonic emissions and cell to cell communication through a clear glass window [45].

The concept of neural communication by photons was further elaborated by Bernroider in 2005 [46] arguing that quantum coherence may be sustained in ion channels long enough to be relevant for neural processes, and that the channels could be entangled with surrounding lipids and proteins and with other channels in the same membrane. Ion channels regulate with electrical potential across the axon membrane, and thus play a central role in the brain's information processing [46]. This author has also proposed that K2P channels are the mechanism for this quantum coherence and the theory involves binding pockets where two K^+ ions are trapped in the selection filter of the closed ion channel.

The theory has been investigated by Sun and colleagues in 2011 [47] who used LED light to stimulate biophoton production and demonstrated the conduction of the biophotons along nerves using "*in situ* biophoton autography"[47] with silver granules. These researchers speculate that these biophotons act as neural communication signals, proposing a protein to protein transmission. They also found that "different spectral light stimulation (infrared, red, yellow, blue, green and white) at one end of the spinal sensory or motor nerve roots resulted in a significant increase in the biophotonic activity at the other end"[47] with sensory nerves more sensitive to infrared and white light and motor nerves more sensitive to red and white light.

4 Conclusion

Current research indicates that a proportion of chronic pain can be associated with dysregulation of ion channels in various parts of the body- peripheral nerves, mitochondria, trigeminal nucleus, DRG and CNS- and that the modulation of these systems may be important in understanding the effect of laser on chronic pain. Research evidence supports the concept of channelopathies as a cause of chronic pain and suggests mechanisms by which laser may act to modulate pain pathways and achieve pain reduction for patients. Current research into the critical role of electrically silent K2P channels in the fine-tuning of excitation of sensory neurons, from the periphery to the cortex, indicates that they play a crucial role in integrating the function of the nervous system. It is thus possible that K2P, and therefore much of the nervous system function, is modulated by hormones and enzymes in the melacortin system as well as neuropeptide molecules. The agents of this modulation are as yet unknown but may possibly involve endogenously produced photons. The mapping outlined here represents a mechanism of laser success in the treatment of unresponsive conditions that exhibit neural dysregulation.

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