Physical Therapy Reviews

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/yptr20

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Ayman A. Mohamed & Motaz Alawna

To cite this article: Ayman A. Mohamed & Motaz Alawna (2020): The use of passive cable theory to increase the threshold of nociceptors in people with chronic pain, Physical Therapy Reviews, DOI: 10.1080/10833196.2020.1853493

To link to this article: https://doi.org/10.1080/10833196.2020.1853493

PHYSICAL THERAPY REVIEWS
https://doi.org/10.1080/10833196.2020.1853493

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The use of passive cable theory to increase the threshold of nociceptors in people with chronic pain

Ayman A. Mohamed[a] and Motaz Alawna[a,b]

[a]Department of Physiotherapy, Faculty of Health Sciences, Istanbul Gelisim University, Turkey; [b]Department of Physiotherapy and Rehabilitation, Faculty of Allied Medical Sciences, Arab American University, Jenin, Palestin

ABSTRACT

Background: Chronic pain is one of the disorders that cost any society high expenses. The major mechanisms responsible for the conversion of pain from acute to chronic are still unclear. One major mechanism of these mechanisms is the hypersensitivity of nociceptors to any noxious stimulus. Treatment approaches for chronic pain have not targeted the abnormal function of nociceptors or achieved long-time relief of pain yet.

Objectives: To outline the effectiveness of passive cable theory to decrease the hypersensitivity of nociceptors in patients with chronic pain and renormalize the abnormal hypersensitivity of nociceptors.

Major Findings: applying the concept of the passive cable theory in the treatment of chronic pain would decrease the hypersensitivity of nociceptors and produce a decrease in chronic pain levels. This could occur through increasing the passive background leakage of ions in the opposite direction against their major flow direction. During the major flow of ions through the cell membrane occurs with any noxious stimulus, a background passive leakage of the same ions occurs in the opposite direction. This leakage helps in increasing the postsynaptic potentials and prolongs their decay phase. In turn, this decreases the hyperexcitability of the central nervous system, which commonly occurs in chronic pain. Both decreases in the peripheral and central sensitization would decrease the depletion of β-arrestin-2, which leads to a decrease in the descending painful mechanism.

Conclusion: The use of passive cable theory would be a useful intervention to decrease the hypersensitivity of peripheral nociceptors and hyper-excitability of the central nervous system, which are common mechanisms of persisted chronic pain. This helps to renormalize the abnormal mechanism commonly occur in chronic pain and would cause a prolonged decrease in chronic pain.

KEYWORDS
Chronic pain; nociceptors; passive cable theory; threshold

1. Introduction

Chronic pain costs any society high expenses and significantly affects the functional, social, and psychological states of its people [1–3]. The causes, mechanisms, and treatments of chronic pain are unclear yet [3]. Interestingly, about 80% of the causes of chronic pain are none specific [4]. Chronic pain represents the greatest challenge for researchers and clinicians to find effective treatment approaches to manage this long-standing pain and configure the mechanisms that cause the transition of pain from acute to chronic [5]. The change of pain from acute to chronic depends more on maladaptive changes that occur in the pain-sensing and processing mechanisms and the period of the pain [5–7]. Also, it has been demonstrated that acute pain can present for an extended period without ever experiencing a 'chronicization' of its basic mechanisms [8,9].

One of the major maladaptive changes in the pain-sensing and processing mechanisms and is mainly responsible for the chronicization is the abnormal changes that occur in the normal physiological function of nociceptors [5,10]. It has been found that nociceptors undergo an increase in their sensitivity and a decrease in their threshold (peripheral sensitization) [10]. The peripheral sensitization is defined as the drop in the threshold and/or the rise in the level of responsiveness of the peripheral terminals of sensory nerve fibers [11]. This happens due to the presence of chemical mediators secreted by nociceptors and non-neuronal cells (e.g. fibroblasts, keratinocytes, neutrophils, mast cells, basophils, platelets, macrophages, and endothelial cells) at the site of tissue inflammation or injury [11]. These chemicals cause an increase in the nociceptors' sensitivity to any small painful stimulation causing the patients to feel pain from even non-painful stimuli [10].

CONTACT Ayman A. Mohamed amohamed@gelisim.edu.tr Department of Physiotherapy, Faculty of Health Sciences, Cihangir, Şehit Jandarma Jandarma Komando, Er, J. Kom. Er Hakan Öner Sk. No: 1, Avcılar, 34310, İstanbul, Turkey.

Pharmacological approaches for treating pain have included the administration of opioids to manage chronic pain [12,13] or the injection of some chemicals in the pain site to decrease the sensitivity of nociceptors [14,15]. The administration of opioids remains controversial due to the concerns about their long-term effectiveness, side effects, functional outcomes, or potentials for drug abuse and addiction [16]. According to the Centers for Disease Control, approximately 91% of Americans die from opioid overdose each day [17].

On the other side, non-pharmacological approaches for treating of pain have included patient education, massage, traction, superficial heat/cold, electrical stimulation, low-level laser therapy, and lumbar supports … etc. Also, there are insufficient data to draw firm decisions on their clinical effects for decreasing chronic pain [18]. The use of supra-threshold painful stimulation (counter-irritation) is another non-pharmacological approach used to manage chronic pain. It refers to the application of an extreme stimulus on the painful area or another distinct area of the body to relieve pain [19,20]. This supra-threshold stimulation can be applied by using intense transcutaneous electrical nerve stimulation (TENS), topical capsaicin, heat, or cold. However, these methods can provide short-term effects in decreasing chronic pain which increases the difficultly of building up a firm conclusion about the effectiveness of these methods to suppress chronic pain for a long time [20]. Neuromodulatory treatments (rTMS and tDCS) have achieved good results in decreasing chronic pain; however, Their effects and mechanism of action are still unclear and may be associated with adverse autonomic effects [21,22]. Patients also may experience a headache after Neuromodulatory treatments application, especially over the triggered areas [21,22].

Recently, there is a novel direction has been developed to decrease the sensitivity of hyper-responsive organs or areas by using a theory called passive cable theory. This theory states that applying a subthreshold stimulation to any system that has ionic channels to decrease its sensitivity and increase its threshold [23–25]. Despite the benefits of this treatment, to the best of our knowledge, there are no previous studies have investigated the effect of subthreshold painful stimulation on decreasing pain sensitivity and elevating the pain threshold. Applying subthreshold stimulation could be also, beneficial in decreasing the suffering of people with chronic pain who have to tolerate supra-threshold methods to relieve their chronic pain.

Thus, this review was conducted to suggest a novel direction in the treatment of chronic pain by decreasing the hypersensitivity of nociceptors in people with chronic pain. For a better understanding of this direction, this review is subdivided into three main subtitles including, the abnormal changes in the nervous system with chronic pain function with chronic pain, the current modalities for the management of chronic pain, the passive cable theory theoretical and practical bases.

2. The abnormal changes in the nervous system with chronic pain

2.1. The abnormal changes of nociceptors in chronic pain (peripheral sensitization)

Nociceptors are peripheral receptors in the nociceptive system that respond to any noxious stimulus. Nociceptors can be divided into three main types including; mechanical, chemical, and thermal sensory nociceptors [26]. The cell bodies of nociceptive sensory neurons present in the dorsal root ganglia (DRG), and synapse at superficial spinal dorsal horns [26].

Nociceptors contain various ion channels that mediate the transmission of physiochemical substances through transient receptor potential (TRP) channels [26]. These TRP channels include three main specific types. The first type includes TRPV1 and TRPV2, calcium-gated chloride (Ca2+-gated Cl–), and anoctamin channels. These channels are responsible for sensing warm and hot temperatures [27,28]. The second type includes TRPA1, the ATP-gated purinergic ion-channels (P2X3 andTRPM8), and sodium ion channels (Nav). These channels are responsible for cold-associated pain transduction [29,30]. The third type includes Piezo1 and Piezo2 channels. These channels are responsible for the transduction of mechanical stimuli [31]. The activation of TRP channels causes a generation of transient potential. However, this transient potential can stimulate sodium (Na+) channels such as Nav1.8 and Nav1.9 channels [32], a counteracting endogenous inhibition occurs to modulate this stimulation by activating potassium (K+) channels such as the two-pore channels TREK1 and TRAAK1 [33]. If the stimulation exceeds this inhibition mechanism, the action potential occurs, and travel from peripheral nociceptors to the central nervous system [32,34].

The nociceptors are hypersensitive in chronic pain, (peripheral sensitization). This hyper-sensitization of nociceptors occurs in response to some chemical substances released in the site of injury. This peripheral sensitization is mediated by various chemical substances including (prostaglandins [PGE2], glutamate. protons, endocannabinoids, ATP, thromboxanes, leukotrienes, and growth factors such as neurotrophins) [10,28,35,36]. These

chemical substances help in modulating the transduction of proteins.

Proteins play a major role in controlling nociceptors' excitability at the transcriptional or post-transcriptional levels [28,36–38]. G-protein coupled receptors (GPCRs) also have a basic role in the peripheral sensitization process. Recent studies have shown that Gq/G11 has a critical role in nociception *in vivo* as they are the bases of abnormal nociception, development of acute pain, and spans sensitization mechanisms in pathological pain state s [39]. In sensory neurons, GPCRs are activated by a diverse set of metabolic products, peptides, and bioactive lipids. GPCRs can couple with various G-proteins: Gq, G11, Gs, Gi, G12, or G13. G-proteins (Gq/G11) can mediate the activation of phospholipase C-β (PLC-β), protein kinase C (PKC), the release of Ca2+ from intracellular stores, and modulation of extracellular regulated kinases (ERK1, ERK2) [40]. In the peripheral sensitization, these G-protein coupled receptors bind to cAMP–protein-kinase-A (PKA)-causing an abnormal function of these receptors [41].

2.2. The abnormal changes in the central nervous system in chronic pain (central sensitization) and other systems

The persistent hypersensitivity of nociceptors causes a sensitization of the central nervous system too (central sensitization). The hypersensitivity of N-methyl-D-aspartate receptors (NMDARs), which is a type of the nociceptors, in chronic pain mainly causes this central sensitization [42,43]. In normal conditions, NMDAR channels are blocked by Mg^{2+} ions. In the presence of any noxious stimulus of sufficient intensity, the blockade for Mg^{2+} terminates. The stimulation of NMDAR increases the Ca^{2+} influx which increases the synaptic firing [44]. The influx of CA^{2+} triggers intracellular signaling pathways. In the presence of persistent tissue or nerve injury, this activation continues and the central sensitization occurs. In chronic pain, there is an increase in the expression of the NMDAR-NR2B (GluN2B) subunits, which controls the spinal synaptic plasticity [44]. This NR2B/GluN2B receptor activity is adversely controlled by β-arrestin-2 [45]. The decrease in β-arrestin-2 causes the secretion of opioid substances, such as morphine and encephalin. The continual loss of β-arrestin-2 causes a prolongation of pain. Thus, even with the hypersensitivity of nociceptors, no further decrease in the pain occurs because β-arrestin-2 is depleted causing a more decrease in the secretion of opioid substances [46].

The persistent activity of peripheral nociceptors causes several changes in other systems. The persistent activity of peripheral nociceptors stimulates several synapse-to-nucleus messengers (including signal transducers and transcription activator 3 'STAT3' and mitogen-activated protein kinase 'MAPKs') as an attempt to control this hyperactivity through stimulating the descending pain mechanism [26]. This leads to more depletion of opioids and the development of pain occurs again [26,47,48]. Also, Dorsal root ganglion (DRG) neurons are found to have a critical role in stimulating and exciting the cell-to-cell interactions process in chronic pain [49,50]. The DRG neurons are the primary neurons of the sensory system. They are stimulated by numerous sensory stimuli to send impulses to the central nervous system about the nature of this stimulus [51]. The abnormal DGR function causes abnormal changes in non-neural cells such as T cells and neutrophils which decrease the cell-to-cell interactions process [52]. In chronic pain, spinal glial cells in DRG are stimulated causing neuropathic pain development by secreting numerous signaling molecules such as pro-inflammatory cytokines and chemokines. These molecules cause neuronal hyperexcitability [52].

There is a strong relationship between immune cell categories (e.g. neutrophils, mast cells, macrophages, and T cells) and immune-like glial cell categories (e.g. satellite glial cells, Schwann cells, and astrocytes and microglia) to neuropathic pain after nerve injury [53]. Mast cells that live in the nerve degranulate at the location of nerve injury and secrete painful mediators such as histamine, proinflammatory cytokines, or prostaglandins. Equilibrium of mast cells with sodium cromoglycate inhibits the occurrence of hyperalgesia and decreases the stimulation of monocytes and neutrophils to the site of nerve injury [54]. Substantial infiltration of neutrophils at the location of nerve injury and the DRGs of the same side has been detected after peripheral nerve injury [52].

3. The current modalities in the management of chronic pain

The treatment of chronic pain is still a big challenge and clinicians still struggle with this type of pain. Despite the well-studied and documented abnormal nociceptive changes that occur due to chronic pain, there is no clinically used effective method to target these changes [55]. The used approaches to managing chronic pain can be subdivided into pharmacological and non- pharmacological approaches.

3.1. Pharmacological and invasive treatment approaches to chronic pain

Pharmacological approaches have included either non-invasive medications or invasive procedures. Clinicians usually have used several medications to manage the pain including non-steroidal anti-inflammatory drugs, weak and strong opioids, topical analgesics, and adjuvants [12]. However, these medications are relatively safe, cheap, and fast for the management of chronic pain [12], they have achieved 30% relief of all chronic pain conditions [13].

Another challenge in using these medications for the management of chronic pain is that according to the World Health Organization, the dose of oral administration of these analgesics should be increased gradually until the achievement of pain relief [13]. It might indicate that after a certain time, patients cannot take these analgesics and pain occurs again and no further decrease in pain occurs. Furthermore, these analgesics might predispose patients to some serious systemic side effects and drug withdrawal signs. Besides, there is no quality evidence for the use of these analgesics for chronic pain management [56–60].

The invasive procedures used to manage chronic pain have included implantable drug delivery systems, nerve block injections, denervation surgeries, and nerve stimulators. All these procedures have not been supported by the WHO. Also, some authors have indicated that these invasive procedures can be added to the WHO later as the last step for patients who don not respond to the administration of different types of analgesics. Moreover, these procedures are harmful and can predispose the patients to a high degree of infection and more severe complications [14,15].

3.2. Non-pharmacological and invasive treatment approaches to chronic pain

On the other side, non-pharmacological approaches to manage chronic pain have included supra-threshold stimulation, deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), spinal cord stimulation (SCS), transcranial direct current stimulation (tDCS), and exercises. Supra-threshold modalities include the use of topical capsaicin, heat/cold, or intense TENS. Capsaicin mainly consists of peppers that can be externally applied as a pitch or cream. Capsaicin itself is painful and works as a counter-irritant by replacing or distracting current pain by another more intense pain [61]. However, using capsaicin to decrease chronic pain is widely used, dysfunction may occur to nociceptors after repeated use of capsaicin because the patient experiences prolonged desensitization to a noxious stimulus which causes a loss of nerve function [62]. Moreover, it has been demonstrated that it is very difficult to gather good quality evidence for the use of capsaicin [61].

Heat and cold (thermotherapy, cryotherapy) applications have demonstrated significant pain relief; however, this relief lasts only for a short time [63]. Thermotherapy can indirectly reduce pain by decreasing muscle spasm and increasing the local circulation leading to short-term pain reduction [64]. Cryotherapy also can achieve pain reduction by decreasing muscle temperature, and local metabolism *via* decreasing muscle activity and nerve conduction velocity [65,66].

Transcutaneous electrical nerve stimulation is the primary method usually used by clinicians to manage acute and chronic pain [67]. Transcutaneous electrical nerve stimulation is a therapeutic method applied through the skin using adhesive electrodes over certain areas of skin [68]. Transcutaneous electrical nerve stimulation (TENS) delivers a pulsed electrical stimulation with a modified intensity and frequency. However, TENS has achieved significant results in relieving acute pain, its effectiveness in relieving chronic pain might be restricted by the development of tolerance to TENS after several applications [69]. Recently, Wu et al. [70] performed a meta-analysis to document the effectiveness of TENS for treating chronic low back pain. They found that TENS did not decrease signs and symptoms of lower back pain, and it can be used only in producing short-term enhancement in the functional disability.

Additionally, Gibson et al. [71] performed an analysis of the evidence on the effect of TENS in treating chronic low back pain. They found that there was a very low quality of the evidence, and the whole number of participants included in the analyzed studies was small. They concluded that no firm conclusion could be drown on TENS-associated side-effects, TENS-related effects on patients' disability and health-related quality of life, or TENS-related improved physical and psychological conditions of people with chronic pain.

Deep brain stimulation also is another available method for the treatment of chronic pain [72]. The mechanism of DBS depends on stimulating the brain structures (the periventricular grey matter and lateral somatosensory thalamus) to interfere with the regulation of nociceptive signaling and transmission. This can be performed by using a noninvasive device called a neurostimulator (occasionally mentioned as a 'brain pacemaker'). This device sends electrical impulses, throughout fixed electrodes, to particular targets in the brain [73]. However, DBS

has been used to decrease chronic pain, it is a high-risk procedure and it is still under investigation since the 1950s. Besides, it should be applied with high caution on carefully selected people. It has been demonstrated that DBS can achieve pain relief in only 50% of patients who used DBS to manage their pain [74,75]. The main mechanisms of DBS are still not fully clear and it can cause several hazards due to the high variability in its application methodology [74].

Repetitive transcranial magnetic stimulation and transcranial direct current stimulation are two other techniques that have been used to decrease chronic pain. They are non-invasive brain stimulation methods that stimulate certain areas in the brain cortex by delivering an electromagnetic force *via* placing equipment over the skin on the head [76]. Pieces of evidence have indicated that rTMS and tDCS can achieve a pain reduction in people with fibromyalgia when used for 20 min for several repetitive sessions over the motor cortex. The effects of tDCS and rTMS are still under investigation and their mechanism of action is still unclear and may be associated with adverse autonomic effects [21,22]. Furthermore, advanced modalities such as magnetic resonance imaging, stereotactic computerized tomography, and brain atlas should be used for accurate target localization of electrodes into the subcortical cerebrum which must be applied under local anesthesia [21,22]. Patients also may experience a headache after the application of rTMS and tDCS, especially over the stimulated areas [21,22].

Spinal cord stimulation (SCS) is another method that has been used to manage chronic pain [77]. Spinal cord stimulation decreases the spinothalamic tract activity by delivering an electrical field to the dorsal column axons in the dorsal horn. This can be performed through placing electrical stimulation electrodes on spinal nerves in the epidural space, thus paresthesia occurs over myotomes of targeted nerves [77,78]. Despite that SCS is recommended in the UK as a treatment for chronic pain, SCS is very expensive and has some critical risks and complications [79,80]. Previous studies have reported that to obtain an adequate anesthetic effect to a painful body area, the leads of SCS should completely cover this area. Thus any small movement or displacement of leads during the application of SCS may change the covered area causing unwanted sensory and motor signs [80]. Furthermore, SCS stimulation could elicit various undesired autonomic and viscero-somatic reflexes at various levels [80].

Some exercises have been performed to decrease chronic pain. These exercises aim to maintain and maximize the functional ability without causing an enhancement in the level of pain [81]. These exercises included light aerobic and stretching exercises to regain or increase muscle power, increase the range of motion [18,81]. The effectiveness of these exercises remains limited because they do not target nociceptors themselves. The limited effect of exercises in managing chronic pain is documented by the review conducted by Hayden et al. [82] to study the effectiveness of exercises performed to treat the non-specific back pain. They found that previous exercises slightly reduce back pain [82]. Another type of exercise used to decrease pain is proprioceptive training [83]. Proprioceptive exercise decreases the pain through stimulating mechanoreceptors to block the pain signals which might improve the function, ROM, and balance [84–88]. However, there is no consistent advantage in adding proprioceptive training to neck- and low back pain itself or long-term functional restoration [83].

To overcome the limitations of previous approaches in managing chronic pain, it has been suggested that the treatment of chronic pain should include multidisciplinary treatment including physiological, physical, and medical components to effectively decrease this type of pain. This direction of treatment exists in most pain clinics, however, the patient response to this multidisciplinary management still in debate as the pain becomes chronic [20].

4. The passive cable theory theoretical and practical bases

4.1. The definition of the passive cable theory

It has been demonstrated that nonlinear conductors undergo a theory called the passive cable theory of the biological membrane which indicates that the opening of the ion channels rises ionic permeability and drops membrane resistance [89]. This means that during the major flow of ions, mainly potassium across the cell membrane, a background passive leak of the same ions occurs in the opposite direction [90]. This background leakage could increase the threshold of the stimulation and decreases the sensitivity of the receptors because this leakage helps in boosting the postsynaptic potentials and prolongs their decay phase [89–91].

The passive cable theory plays an important role in defining the electrical properties of neurons which helps in controlling passive membrane properties by leak currents. The leak channels, mainly present in neurons, are the K^+ permeable TASK and Cl-permeable CIC-2 channels. There is also a small contribution from TTX-insensitive, Na^+ permeable NALCN channels [92]. However, leak channels are voltage-independent conductance, leak currents mainly depend on membrane

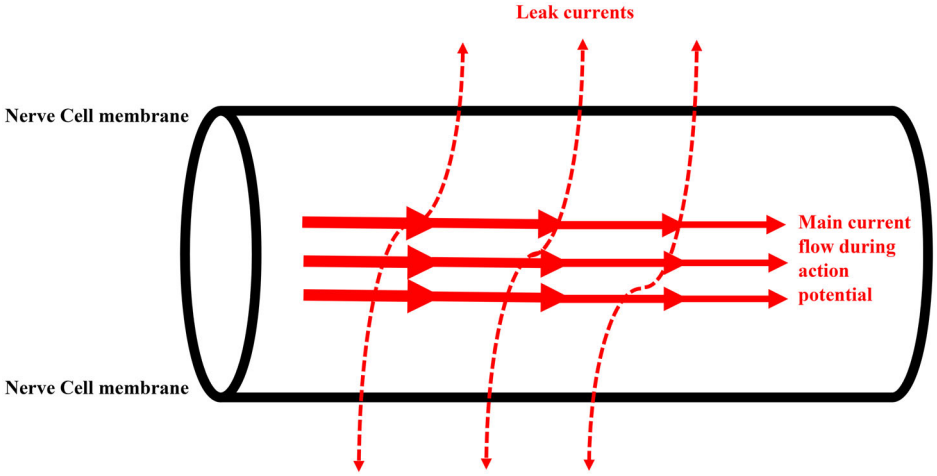

Figure 1. The passive cable theory. Nerves are considered non-linear conductors. Thus, during the flow of current across the axonal membrane through the depolarization of the membrane, not all amount current reaches the end of the nerve. As the current travels down through the axon, some of it leaks out through the membrane before it reaches the end of the axon.

potential. These channels are regulated by electrical potentials of infusing ions and ionic concentration differences. When a concentration gradient is taken into account, the associated electrical current rectifies with the membrane potential. Both these mechanisms help to rebalance membrane potentials [92].

Passive cable theory helps in increasing inward current conductance (the negative slope conductance). The negative slope conductance region occurs when the electrical current is triggered by depolarization which causes positive feedback between the stimulation and the amplitude of the current throughout a reformative mechanism. The stimulation phase of the voltage-gated sodium and calcium currents are considered examples of areas of negative slope conductance. The final result of the negative slope conductance is a net rise in the total membrane impedance [89,93]. Thus, increasing this negative cable conductance can help in increasing the threshold of the neuronal membrane and decrease its sensitivity. The passive cable theory in nerve cell is illustrated in Figure 1.

4.2. The possible effects and applications of passive cable theory

Nociceptors respond nonlinearly to any painful stimulation [94–96]. Morisset and Nagy [95] have demonstrated that nociception signals are long-lasting inputs with prolonged after discharges. These nociceptors have slow activation kinetics and are voltage-dependent [94–96]. These two characteristics cause nociceptive sensory neurons to have non-linear input-output interactions in both the time and amplitude domains. Recently, Dik [94] conducted a bifurcation analysis of a nociceptive neuron model to investigate the alterations in the firing activity pattern due to the application of harmful pain stimulation on the dorsal ganglia of rats. He found that the firing patterns of nociceptive neurons were nonlinear in response to any damaging injury. This nonlinear behavior of nociceptive neurons occurs because they depend on ions diffusion between specific ion channels to initiate and propagate their signals (the action potential) [89]. Due to this nonlinear behavior of nociceptive neurons, they can be considered as nonlinear conductors [89].

Several animal studies have demonstrated that decreasing the activity of nociceptors by injecting some chemicals could decrease the activity of central nociceptive neurons [97–100]. Gjerstad et al. [98] studied the effect of local intramuscular injection of capsaicin on the spinal nociceptive responses in rats. They found that the injection of capsaicin peripherally decreased the activity of spinal nociceptive neurons in the spinal dorsal horn. Li and Chen [99] investigated the effect of peripheral injection of Melittin on spinal neuronal responses in rats. They found that injecting the Melittin into the hind paw of a rat induced a direct, dose-dependent rise in spontaneous spike discharges of spinal dorsal horn wide-dynamic-range neurons. A recent study was conducted by Kakita et al. [100] to investigate the effect of local subcutaneous injection of chlorogenic acid on the nociceptive trigeminal spinal nucleus neurons in rats. They found that the peripheral injection of chlorogenic acid decreased the activity of the nociceptive trigeminal spinal nucleus neurons. Thus, using the subthreshold noxious stimulation could decrease the central sensitization and cause central sedation of chronic pain.

Both decreases in the peripheral and central sensitization can decrease the depletion of β-arrestin-2, which leads to a decrease in the descending painful mechanism [46]. Increasing the build-up of β-arrestin-2 could help in increasing the release of opioids consequently, a decrease in chronic pain occurs. Li et al. [101] has been demonstrated that

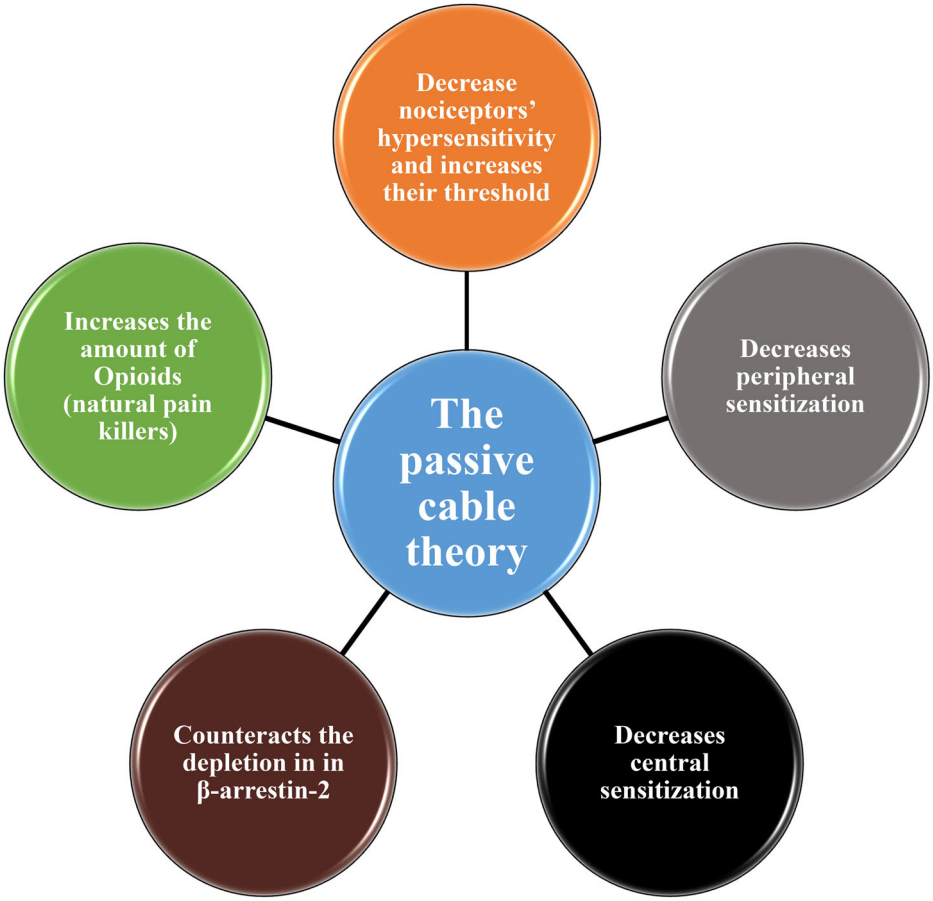

Figure 2. The possible effects of passive cable theory on decreasing chronic pain. Passive cable theory can decrease nociceptors' hypersensitivity and increase their threshold, decrease peripheral sensitization, decrease central sensitization, and count.

the injection of β-arrestin-2 produces a state of analgesia and decreases both acute and chronic pain. Yang et al. [102] have demonstrated also that intrathecal injection of β-arrestin-2 (2 mg siRNA per 10 ml per rat) once daily for 3 days enhances analgesia. Thus, subpainful stimulation could decrease the depletion of β-arrestin-2 which is important to initiate the descending pain mechanism and produce analgesia to chronic pain.

Using the passive cable theory may be a novel alternative intervention to treat chronic pain by increasing the nociceptive threshold of neurons and decreasing their sensitivity. This may occur by increasing the inward leak currents, which increases the membrane resistance. This increase can counteract the hypersensitivity of nociceptors and cause an increase in the threshold of pain and decrease in pain perception for a long time. The decrease in the hypersensitivity of nociceptors could extend to cause a decrease in the hyperexcitability presented in the central nervous system.

The application of passive cable theory could be performed by using subthreshold noxious stimulation for a certain period. Subthreshold intensities can be 79%, 63%, 50%, 40%, or 32%. Lundstrom et al. [103] used 50% of the threshold. Other studies used 90% and 80% subthreshold vibration applied to the mechanoreceptors [104–106]. The application of passive cable theory in rehabilitation can be performed by introducing subthreshold stimulators in braces or splints such as back, neck, or ankle braces to decrease their chronic pain, the advantages of using subthreshold stimulators include that they are painless and can be applied for prolonged periods. Besides, inserting these subthreshold stimulators could help in increasing the effectiveness of these splints or devices because the pain itself can prevent the optimal adjustment of these braces or splints. Consequently, these braces or splints may be called subpainful braces or splints. The possible effects of passive cable theory are shown in Figure 2.

4.3. Other uses of passive cable theory in rehabilitation

Using the passive cable theory could help in decreasing the threshold of any hyperactive nonlinear systems or areas. Lundstrom et al. [103] investigated the effect of applying subthreshold cortical stimulation on decreasing the activity of focal epilepsy. They applied a prolonged subthreshold stimulation on seizure-onset-zones and surrounding areas. They found that subthreshold stimulation-induced a decrease in delta (1–4 Hz) power during

trial stimulation with a correlated improved long-term clinical outcomes. Based on these results, they have suggested that subthreshold cortical stimulation can be considered as an effective alternative treatment for managing focal drug-resistant epilepsy.

A more pain-related study was conducted by Poletto and Van-Doren [25] to investigate the effect of applying pre-pulse subthreshold stimulation. They applied subthreshold stimulation to fingertips using small (1-mm diameter) electrodes. They measured the pain threshold afterward by psychological analysis. They found that long, subthreshold, depolarizing pre-pulse elevated the pain threshold so that the following stimulus pulse was less painful.

In the future, the passive cable theory could be used in the rehabilitation of patients with stroke to decrease spasticity and promote more functional movements. This can be conducted through the application of subthreshold stimulators on the hyperactive cortical region to induce a decrease cortical excitability at the site of stimulation and transsynaptically at distant sites (modulation of excitability).

5. Conclusion

The use of passive cable theory would be a useful intervention to decrease the hypersensitivity of peripheral nociceptors and hyper-excitability of the central nervous system, which are common mechanisms of persisted chronic pain. This helps to renormalize the abnormal mechanism commonly occur in chronic pain and would cause a prolonged decrease in chronic pain.

Disclosure statement

No potential conflict of interest was reported by the authors.

Notes on contributors

Ayman A mohamed is an Assistant Professor at Department of Physiotherapy, Faculty of Health Sciences, Istanbul Gelisim University, Turkey.

Motaz Alawana is an Assistant Professor at Department of Physiotherapy and Rehabilitation, Faculty of Allied Medical Sciences, Arab American University, Jenin, Palestin. He also is an Assistant Professor at Department of Physiotherapy, Faculty of Health Sciences, Istanbul Gelisim University, Turkey.

ORCID

Ayman A. Mohamed http://orcid.org/0000-0001-5092-3549
Motaz Alawna http://orcid.org/0000-0002-4936-373X

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