

**Modulation of Pain through Thermotherapy: An Appraisal of Current
Theories**

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Abstract

Thermotherapy is the use of heat as treatment in pathology and disease, and for many years it has been used in its various forms to relieve pain³. Thermal modalities are useful in the treatment of pain, and they operate at four main levels: peripheral, spinal segmental, supraspinal, and cortical^{3,4}. At a peripheral level, agents are applied in order to locally limit or reduce a noxious stimulus and/or the response of nearby peripheral nociceptors. Local effects include changes in blood flow due to vasodilation; reduction of levels of bradykinin, prostaglandins, and other algogenic substances and mediators; inhibition of the production of the aforementioned elements; and the impediment of conduction of sensory afferents⁴. At the spinal segmental level, agents 'close the pain gate' by stimulating large-diameter A-alpha and A-beta afferent fibers whose conduction speeds exceed those of the smaller A-delta and C-fibers responsible for relaying pain messages. Impulses from the larger diameter afferents reach the dorsal gray horn of the spine first, closing the pain gate to the signals from smaller, more slowly conducting fibers^{5,15}. Activity at the spinal segmental level is also modulated by signals from supraspinal areas via the opioidergic and serotonergic/noradrenergic systems⁴. Endogenous opiates decrease the passage of nociceptive information through the dorsal spinal cord. Thermal agents also excite the supraspinal centers of the nervous system which control descending inhibitory control mechanisms. Descending inhibitory mechanisms involve the release of endogenous opiates at spinal segmental and peripheral levels⁴. Thermal agents acting upon cortical levels interpret sensory messages from the thalamus and

respond by stimulating the supraspinal, spinal segmental, and peripheral levels of the nervous system, respectively.

Objective

The objective of this review is to evaluate the various theoretical mechanisms by which thermotherapy results in pain relief. The gate control theory, theory of descending inhibition, theory of counterirritation, and placebo effect will be discussed in relation to thermotherapy and the role of each the efficacy of each mechanisms theory in terms of their capacity for pain relief will be discussed.

Introduction

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with potential or actual tissue damage¹. Pain is subjective; unlike blood pressure or heart rate, it is difficult to measure pain objectively. Age, gender, physical capability, and social or cultural norms that regulate acceptable pain related behavior are all factors that influence how a person distinguishes and communicates about pain.

Thermotherapy is the use of heat as treatment in pathology and disease, and for many years it has been used in its various forms to relieve pain². Thermal modalities are useful in the treatment of pain, and they influence the nervous system on four separate levels: peripheral, spinal segmental, supraspinal, and cortical^{3,4}. At a peripheral level, agents are applied in order to locally limit or reduce a noxious stimulus and/or the response of nearby peripheral nociceptors. Local effects include changes in blood flow due to vasodilation; reduction of levels of bradykinin, prostaglandins, and other algogenic substances and mediators; inhibition of the production of the aforementioned elements; and the impediment of conduction of sensory afferents⁴. At the spinal segmental level, agents 'close the pain gate' by stimulating large-diameter A-alpha and A-beta afferent fibers whose conduction speeds exceed those of the smaller A-delta and C-fibers responsible for relaying pain messages. Impulses from the larger diameter afferents reach the dorsal gray horn of the spine first, closing the pain gate to the signals from smaller, more slowly conducting fibers⁵. Activity at the

spinal segmental level is also modulated by signals from supraspinal areas via the opioidergic and serotonergic/noradrenergic systems⁴. Endogenous opiates decrease the passage of nociceptive information through the dorsal spinal cord. Thermal agents also excite the supraspinal centers of the nervous system which control descending inhibitory control mechanisms.

Descending inhibitory mechanisms involve the release of endogenous opiates at spinal segmental and peripheral levels⁴. Thermal agents acting upon cortical levels interpret sensory messages from the thalamus and respond by stimulating the supraspinal, spinal segmental, and peripheral levels of the nervous system, respectively.

Objective

The objective of this review is to evaluate the various mechanisms by which thermotherapy produces pain relief. The gate control theory, theory of descending inhibition, theory of counterirritation, and placebo effect will be discussed. Also, the contribution of each to thermotherapy induced pain alleviation will be discussed.

Neurophysiology of Pain Transmission

A sensory receptor is composed of specialized nervous tissue that is sensitive to a particular change in the environment known as a stimulus. Examples of such stimuli include noise and light. Stimuli release physical energy which receptors

convert into electrochemical energy that generates action potentials in associated neurons. These action potentials enable neurons to transmit signals to the brain for processing. A nociceptor is a specialized unencapsulated receptor that responds specifically to the potentially tissue damaging or tissue damaging stimuli. Nociceptors respond to both mechanical and chemical stimuli that consequently trigger the formation and release of chemical substances like prostaglandin, bradykinin, histamine, substance P, and cholinesterase⁴. These substances sensitize nociceptors in and around the area of injury by lowering nociceptors' depolarization thresholds, making it easier for them to be activated and carry impulses. This process is called primary hyperalgesia. After several hours, secondary hyperalgesia occurs as the brain continues to respond to noxious stimuli and the chemicals spread throughout the surrounding tissues, both inducing swelling and increasing hypersensitivity within the afflicted area. Once stimulated, a nociceptor typically releases a neuropeptide called substance P that initiates the electrical impulses that transmit pain messages to the spinal cord. Nociceptors are located in nearly all tissues including skin, bone, muscle, joint capsules, viscera, blood vessels, meninges, and peripheral nerve sheaths. Two types of afferent nerve fibers transmit the impulses of nociceptors from the periphery to the central nervous system. A-delta fibers are thinly myelinated axons and have a conduction velocity of 5-30 meters/second. Pain messages from these fibers are well-localized sensations of sharp, pricking pain. C-fibers are unmyelinated axons whose conduction velocity is 0.5 – 2 meters/second. Pain messages from these fibers are perceived as diffuse, dull, poorly localized^{6,7,8}.

Nociceptors located in the skin are called cutaneous nociceptors. Cutaneous nociceptors may be subdivided into mechanical nociceptors, polymodal nociceptors, and mechanically insensitive afferents. Mechanical nociceptors^{6,7,8} respond to strong mechanical stimuli, but not to heat, irritant chemicals, or extreme cold (in normal skin). Predominantly, it is the myelinated axons of A-delta fibers that transmit the impulses of these nociceptors. Some mechanical nociceptors with C-axons have been found, but little is known about them.

Polymodal nociceptors respond not only to strong mechanical stimuli, but also to noxious heat, irritant chemicals, and at times to strong skin cooling. These are the main type of C-fiber nociceptor in mammalian skin, composing about 90% of all afferent C-fibers^{6,7}. Polymodal nociceptors can be differentiated into A-fiber mechano-heat-sensitive nociceptors (AMHs) and C-fiber mechano-heat sensitive nociceptors (CMHs)^{6,9}. There are two types of AMHs. Type I AMHs have very high heat thresholds, usually 53° C or higher, and they are slowly adapting^{6,10}. Type II AMHs have a substantially lower temperature threshold, usually around 45° C, and a lower conduction velocity than type I AMHs, and they are thought to be the signal of first pain sensation^{6,11}. C-polymodal nociceptors are generally stimulated by potassium, histamine, serotonin, bradykinin, capsaicin, mustard oil, acetylcholine and dilute acids by such means as topical application, intradermal injection, and arterial injection^{6,12}. Finally, mechanically insensitive afferents (MIAs) are made up of A-delta fibers and C-fibers that do not respond to or have

very high thresholds for mechanical stimuli. Some of the cutaneous MIAs may be chemo-specific receptors, while others may respond to intense cold or heat stimuli^{6,13}.

Both mechanical and polymodal nociceptors are located in the subepithelial tissue. Specifically, these nociceptors include A-delta and C-fibers. The majority of A-delta and C-fibers terminate as free nerve endings, and though they do respond to pressure and touch, they respond predominantly to temperature and pain. Thermal sensations merge with and are superseded by pain at an upper temperature of 45° C and a lower temperature of 15° C; so, the comfortable range of thermal sensation is fairly narrow¹⁴.

Axons of A-delta fibers and C-fibers connect nociceptors in the periphery to two distinct spinal cord pathways that conduct pain signals to the somatosensory cerebral cortex. The anterior spinothalamic pathways react to and carry messages incited by coarse touch and deep pressure; the lateral spinothalamic tract (LSTT) responds to temperature and pain related stimuli. The LSTT is composed of first, second, and third order neurons. First order neurons are also labeled primary pain afferents; these afferents may be A-delta or C-fibers. These neurons carry pain signals from peripheral nociceptors through their cell bodies in the spinal dorsal root ganglia (DRG) and on to second order pain neurons in the substantia gelatinosa nucleus of the dorsal gray horn. Second order pain neurons can be either nociceptive specific neurons (NS) or wide dynamic range neurons (WDR).

Nociceptive neurons receive peripheral input exclusively from primary pain afferents. Wide dynamic range neurons receive input not only from primary pain afferents, but also from non-nociceptive primary afferents. Second order pain axons decussate to the contralateral spinal cord and ascend as the LSTT toward the thalamus of the diencephalon. Second order axons pass through the contralateral ventrolateral funiculus in the spinal cord and terminate in the ventral posterolateral (VPL) nucleus of the thalamus. The thalamus is the main relay center for the senses, with the exception of smell. It is also the location of the cell bodies of third order pain neurons. Third order pain neurons relay their impulses to the ipsilateral primary somatosensory cortex of the parietal lobe where sensory information is not only interpreted, but also, it is integrated with past experiences and emotions that determine the pain experience⁴.

The gate control theory, descending inhibition theory, counterirritation theory, and placebo theory may be evaluated in terms of their efficacy regarding neurophysiological mechanisms. Further analysis will help to substantiate their physiological efficacy.

Gate Theory

The gate theory of pain modulation was proposed in 1965 by Melzack and Wall¹⁵. This theory maintains that certain stimuli 'open the gate' to noxious sensation, and other stimuli 'close the gate' leaving the body less capable of experiencing noxious sensation. Painful sensory input carried by A-delta and C-fibers open the

gate; the greater the amount of stimulation, the greater the pain sensation.

Conversely, the pain gate may be closed by stimulation of large-diameter afferent fibers.

Large-diameter A-alpha and A-beta afferent fibers are mid-to-heavily myelinated, fast-conducting mechanoreceptors that carry impulses from 30 m/s to 120 m/s, respectively⁴. (Note: Galea did an average of conduction speeds, instead of giving the broad range as determined by amount of axon myelination). A-alpha large-diameter afferents are sensitive to stimuli related to changes in body position, or proprioception, as well as joint vibration. A-beta afferents are sensitive to mechanical stimuli like crude and discriminative touch, but not to heat, cold, or chemical irritants. A-beta afferents are more relevant to gate theory physiology as they are more plentiful in and around the cutaneous A-delta and C-fibers and are more easily stimulated to help reduce pain. However, stimulation of both A-alpha and A-beta afferents are proposed to block the pain signals carried through the dorsal gray horn of the spinal cord by the smaller diameter A-delta and C-fibers. First-order A-delta and C-fibers conduct impulses to the first, second, and third Rexed's laminae in the dorsal gray horn as afferent first-order neurons. A-delta fibers conduct signals specific to the first and third laminae, and C-fibers conduct signals specific to the second lamina⁶. These first-order pain neurons synapse with second-order neurons within the substantial gelatinosa nucleus. Most second order axons cross to the contralateral ventrolateral white column to ascend to the ventral posterolateral nucleus of the thalamus. Here, they

synapse with third order sensory neurons whose axons terminate in the parietal lobe's somatosensory cortex.

A-beta afferent fibers bypass these laminae and carry signals directly into the fourth and fifth laminae. Their first order axons do not synapse in the dorsal horn, but rather, they pass ipsilaterally up the dorsal white column of the spinal cord to eventually reach the gracile and cuneate nuclei in the lower medulla oblongata of the brainstem before synapsing with the second order neurons. The second order neurons are then relayed to the thalamus. In the thalamus of the diencephalon, the sensory pathway for proprioception and discriminative touch continues by synapsing with third order neurons. These neurons ultimately terminate in the somatosensory cerebral cortex (Brodmann's areas 3, 1, and 2 of the parietal lobe). The collaterals of A-beta afferent fibers terminate on the terminals of A-delta and C nociceptor fibers. When they are stimulated, these collaterals excite, to some degree, the A-delta and C-fibers. More specifically, the C-fibers within lamina two, also known as the substantia gelatinosa nucleus, are stimulated. As a result, these fibers' level of excitability to noxious stimuli is lowered. Consequently, when they receive nociceptive input, the quantity of neurotransmitter they would have released to propagate the impulse further is significantly reduced or completely eliminated¹⁵.

To exemplify the gate theory at work within the context of real life, consider someone experiencing pain from some noxious stimulus – someone who has

banged his elbow, for example. His A-delta and C-fibers are stimulated by this noxious stimulus and are transmitting pain impulses to the brain; the pain gate is open. To overcome these impulses, he rubs his elbow. Rubbing his elbow stimulates the A-beta mechanoreceptors whose axon collaterals synapse with A-delta and C-fiber receptors within the dorsal gray horn laminae and stimulate them somewhat. By stimulating these fibers, the A-beta afferents cause them to release their neurotransmitters¹⁶. Though the noxious stimulus is still present, it is not as powerful because there is less neurotransmitter to initiate the impulse. The pain gate is masked or “closed.” Also, because the conduction speed of A-beta afferents are quicker than those of A-delta and C-fibers, signals from A-beta afferents reach the dorsal gray horn of the spinal cord first, resulting in a transmission to higher brain centers that inhibits the transmission of signals from A-delta and C-fibers⁷.

Large diameter A-alpha and A-beta afferents are responsible for proprioceptive and mechanical touch sensation, respectively. How, then, does heat interact with such afferents to assuage pain within the context of the Gate Control Theory? Just as A-alpha and A-beta afferents effectively close the pain gate and hinder the transmission of A-delta and C-fibers, so also may A-delta and C-fibers interfere with one another to afford the brain the capability to perceive various levels of pain from the periphery. It is this interference that may provide thermotherapy with the ability to open and close the pain gate. Consider, for example, A-delta fibers or C-fibers transmitting pain impulses from noxious, non-thermal stimuli to

second and third order neurons in the brain. If, concurrently, thermoreceptors become excited by a thermal stimulus that approaches noxious levels (45° C), the thermal signals will merge with and change to pain signals carried by the A-delta and C-fibers capable of conducting noxious thermal sensation^{14,18}. In theory, the semi-noxious heat stimulus would override, or ‘close the gate’ on the noxious sensation already being transmitted by the A-delta and C-fibers. Also, stimulating the primary pain afferents with such a thermal stimulus leaves the fibers in a refractory state, and any pain stimulus conducted directly after would elicit the release of a reduced amount of neurotransmitter. This would limit the degree of noxious impulses generated, and so reduce noxious information traveling rostrad to the brain. This interaction is known as pre-synaptic inhibition¹⁹. Reducing the nociceptive signals from other C-fibers, as well as outnumbering the input of pain signals along the A-delta fibers effectively closes the pain gate.

Current research seemingly offers no definitive, direct connection between stimulation of large-diameter A-alpha and A-beta fibers and their ability to decrease pain via the gate theory utilizing thermotherapy. To date, there are no studies to prove/support that heat excites the A-beta fibers responsible for inhibiting pain signals from A-delta and C-fibers⁵.

Theory of Descending Inhibition

While the gate control theory explains the inhibition of noxious impulses within afferent pain pathways, the descending inhibition theory describes inhibition of

noxious impulses via efferent pathways. Both exert their influence in the dorsal horn of the spinal cord. The theory of descending inhibition was first investigated in 1969 by Reynolds²⁰, who successfully revealed the role of the midbrain PAG in nociceptive control and found that the stimulation of distinct regions of the brain could generate analgesia. It essentially posits that structures in the brain send descending impulses onto the spinal cord during periods of hyperexcitability brought on by inflammation and injury in the periphery; these impulses inhibit the transmission of pain signals at the dorsal horn^{21,22,23}.

Descending impulses are conveyed through the brain's periaqueductal gray matter (PAG) which projects to the rostral ventromedial medulla (RVM). The caudal PAG may be divided into ventrolateral, lateral, dorsomedial, and dorsolateral columns^{24,25}. Both the ventrolateral and lateral columns play a key role in modulating pain perception, though they inhibit pain transmission with two different mechanisms^{24,25}.

Excitement of the ventrolateral PAG region produces an analgesic effect which may be suppressed by naloxone, an opiate receptor blocking agent, specifically within the dorsal raphe nucleus of the brainstem^{24,26} suggesting that the form of analgesia it generates is of an opioid form. Ventrolateral PAG analgesia seemingly necessitates an extended period of peripheral stimulation before it becomes evident^{24,27}.

Analgesia produced by the lateral PAG is related to fight or flight reactions of the sympathetic nervous system^{24,28,29,30}. This analgesia is not obstructed by naloxone^{24,26} and is consequently defined as non-opioid analgesia. Analgesia following stimulation of the lateral PAG is more rapid than analgesia following stimulation of the ventrolateral PAG.

The rostral ventromedial medulla (RVM) includes the nucleus raphe magnus (NRM), the nucleus gigantocellularis pars alpha, and the nucleus paragigantocellularis lateralis^{21,31}. From the PAG, projections move from the ventrolateral column to the nucleus raphe magnus, and they are termed serotonergic because they use serotonin (5-hydroxytryptamine) as a neurotransmitter. Similarly, projections from the lateral column of the PAG pass to the nucleus gigantocellularis pars alpha, and the nucleus paragigantocellularis lateralis are recognized as noradrenergic because they use noradrenaline as a neurotransmitter. The serotonergic system plays a significant role in mediating analgesia combating thermal nociceptive stimuli, while the noradrenergic system only mediates analgesia combating mechanical nociceptive stimuli³².

Serotonergic pathways exert descending influence on the dorsal horn via endogenous opioids^{21,33}. Opioids are pain-relieving chemicals, of which morphine is an example. Endogenous opioids are opiate neuropeptides which are, unlike morphine, produced by the body within the pituitary gland; they resemble opiates in their ability to produce analgesia and a sense of well-being.

Endorphins, dynorphins and enkephalins are examples of endogenous opioids.

Castel's model suggests that the PAG and nucleus raphe magnus are stimulated by noxious impulses from ascending primary pain afferents. The PAG excites the nucleus raphe magnus which utilizes serotonergic efferent fibers to transmit signals to enkephalinergic interneurons located within the second lamina, or substantia gelatinosa, of the dorsal horn. These enkephalinergic interneurons are stimulated, and they release enkephalin. Enkephalinergic interneurons synapse with A-delta and C-fibers which enkephalin consequently inhibits. It is unclear as to whether or not the noradrenergic pathway triggers this process.

Noradrenergic neurons project from the locus coeruleus within the pons of the brainstem. When stimulated, they release noradrenaline which inhibits activity of nociceptive neurons directly, unlike the serotonergic neurons which inhibit nociceptive neurons indirectly via enkephalins. Little more is known of noradrenergic pathways.

Yet, the release of endogenous opioids is not necessarily dictated by efferent neural pathways and enkephalinergic neurons. The stimulation of A-delta and C-fibers is thought to bring about the release of endogenous opioids directly into the bloodstream from the anterior pituitary gland, the PAG, rostroventral medulla, and the dorsal horn itself²¹. In fact, detection of endogenous opioids within cerebrospinal fluid or blood plasma is used to establish whether or not descending inhibition pathways are activated³⁴. Beta-endorphin (BEP) and dynorphin are two

key endogenous opioids released in such a fashion. Their half-lives are one minute and two minutes, respectively. Residual amounts of such endogenous opioids within the bloodstream provide definitive support of the efficacy of descending inhibition.

BEP is derived from the prohormone proopiomelanocortin and adrenocorticotropin - two substances integrated within the anterior pituitary gland. Stimulation of A-delta and C-fibers for periods of twenty to forty minutes is believed elicit the release of BEP from the anterior pituitary². Also, BEP can be found within the neurons that project from the hypothalamus into the PAG and noradrenergic nuclei in the brainstem. BEP may be released by these neurons upon stimulation of the hypothalamus^{21,35}.

Dynorphin is a lesser known endogenous opioid, recently determined to originate within the PAG, rostroventral medulla, and dorsal horn, respectively^{21,36}.

Thermotherapies are proposed to decrease pain through descending inhibition. In a manner similar to that of the gate control theory, thermoreceptors are excited by a thermal stimulus that approaches noxious levels (45° C), and the thermal signals merge with and change to pain signals carried by the A-delta and C-fibers which are capable of conducting noxious thermal sensation^{14,18}. These A-delta and C-fibers share the same afferent pathways which excite the PAG and initiate the descending inhibition mechanism. Stimuli which are strong enough on noxious levels excite A-delta and C-fiber afferents; this stimulation has been shown to

reduce the output of these neurons in response to painful stimuli within the spinothalamic tract^{34,37,38}. Excitement of these afferents consequently increases the firing rates of the neurons of the PAG and nucleus raphe magnus. Boosting the rates of impulse of the nucleus raphe magnus resultantly increases signals to enkephalinergic interneurons in the dorsal horn of the spinal cord, leading to the release of enkephalins and a subsequent inhibition of painful impulses. Yet, extremely high temperatures are required to produce enough thermal sensation to effectively activate a sufficient amount of afferent fibers¹⁴.

Theory of Counterirritation

Counterirritation may be described as masking or inhibiting pain with another sensation³⁹. Numerous counterirritants are topically applied in the form of ointments, creams, gels, and sprays that chemically stimulate sensory receptors in the skin⁴⁰. These products irritate the skin and generate a mild inflammatory response which subsequently alleviates pain in joints and muscles⁴¹. Specifically, this inflammatory response initiates a local release and subsequent depletion of inflammatory substances like substance P⁴².

Counterirritants are typically composed of one or more main ingredients: menthol (peppermint), methyl salicylate (wintergreen oils), camphor (camphor wood), and capsaicin (chili peppers). Capsaicin is the best researched of the four substances. A review paper by Hautkappe, et. al., concluded that capsaicin effectively reduces chronic pain. This review searched MEDLINE for reports relating to capsaicin,

and uncovered 33 such reports. The data from such reports were analyzed and the level of effective pain relief evaluated, ultimately showing capsaicin effective in temporary pain relief.

Chemical irritants qualify as potential counterirritants due to their ability to stimulate polymodal nociceptors^{43,6,45,46,47,48,39}. Polymodal nociceptors include both A-delta nociceptors, also known as A-mechano-heat nociceptors, and C-fiber nociceptors. A-delta nociceptors respond chiefly to mechanical and thermal stimulation, though they do respond to chemical agents like bradykinin and prostaglandins. However, it is the C-polymodal nociceptors that respond to thermal, mechanical, and chemical stimuli^{6,12}.

Evidence suggests that chemical irritants like menthol, methyl salicylate, camphor, and capsaicin activate temperature-gated ion channels within a subset of primary afferent neurons^{49,50,51}. Specifically, these ion channels are members of the transient receptor potential (TRP) family, and they are known as thermoTRPs. ThermoTRPs are unique in that temperature alone can influence them; they respond to both heat and cold. ThermoTRPs specific to heat stimuli are dubbed TRPV receptors, and thermoTRPs specific to cold are dubbed TRPM and TRPA receptors^{43, 52}.

A total of six heat sensitive thermoTRPs have been identified: TRPV1, TRPV2, TRPV3, and TRPV4. TRPV1 receptors are the most significant in relation to

counterirritants, as they are affiliated with small diameter cell bodies that supply C-polymodal nociceptors⁴⁹. TRPV1 receptors are activated by temperatures above 43° C, the approximate threshold of heat related pain at the skin's surface^{52,53,49}. Counterirritant chemicals like camphor and capsaicin, for example, also activate TRPV1 receptors by increasing membrane permeability to Na⁺ and Ca²⁺ ions, specifically targeting C-polymodal nociceptors⁵⁴.

Two cold sensitive thermoTRPs have been definitively identified within the TRPM and TRPA families: TRPM8 (also called CMR1) and TRPA1 (also called ANKTM1)^{55,56,49}. TRPA1 is most likely to be involved with counterirritants and nociception because its temperature threshold for activation is approximately 17° C, the temperature threshold for cold nociceptors^{57,49}. TRPM8 is expressed in neurons that can be categorized as small diameter C-fibers^{58,59,60,49}. TRPA1 is expressed by a subset of sensory neurons that express the nociceptive markers CGRP and substance P^{61,49}. TRPA1 receptors are often coexpressed with TRPV1 receptors, suggesting both receptors function to mediate the same class of polymodal nociceptors (C-fibers). Counterirritant chemicals like menthol and methyl salicylate activate these receptors. Menthol activates TRPM8 receptors at temperatures of approximately 25° C to 28° C. TRPM8 is a nonselective cation channel with relatively high Ca²⁺ permeability, and it shows a similar current-voltage relationship to TRPV1, suggesting similar functional mechanisms⁴⁹. TRPA1 has a lower activation threshold than TRMP8; temperatures of 17° C or lower are required to activate this ion channel. In a study performed by Jordt et

al.⁶² in 2004 failed to establish a direct connection between cold sensation and TRPA1 receptors, but a study by Jordt et al.⁶² and Bandell et al.⁶³ later in 2004 illustrated the activation of TRPA1 channels by isothiocyanate compounds. These findings suggest a more direct correlation between chemical activation via cooling compounds and TRPA1 channels as opposed to definitive temperature related stimulation.

The mechanisms of counterirritants that produce pain relief are not widely understood, but evidence suggests counterirritation could operate via activation of peripheral inhibitory mechanisms, spinal segmental inhibitory mechanisms, as well as supraspinal inhibitory pathways that influence nociceptive stimuli^{64,65,66,67,39}.

Evidence suggests counterirritants first affect the body peripherally. They specifically target thermoTRPs on C-polymodal nociceptors. They excite these nociceptors by altering the conductance of the ion channels in the cell membranes, ultimately causing depolarization⁶⁸. C-polymodal nociceptors contain neuropeptides like substance P, CGRP, and bradykinin. Counterirritants generate a mild, local inflammatory response which subsequently elicits the release of the aforementioned chemical agents^{16,17}. Studies of TRPV1 receptors in rats suggest that these receptors are modulated by such agents⁵⁶.

Substance P is believed to be responsible for the burning sensation associated with counterirritants⁶⁹. It excites TRPV1 receptors and opens the ion channels, keeping them open and consequently propagating the transmission of thermal sensations to the brain. Upon its release, substance P continues to stimulate these receptors and subsequently sustains perceived thermal sensation. However, substance P is eventually expended, temporarily disabling the nerve⁴². Thus, in addition to the counter-irritation produced by thermal sensation, presynaptic inhibition also helps reduce pain at the site of injury by first initiating the release of substance P, enhancing the inflammatory response, and then depleting it, consequently hindering the inflammatory response.

Theory also suggests that counterirritants exhibit spinal segmental inhibitory effects via a modified definition of the gate control theory. Counterirritants stimulate the chemical receptors on C-polymodal nociceptors, and those sensations are transmitted through the dorsal horn of the spinal cord and into the spinothalamic pathway. The chemical and thermal impulses generated by counterirritants are allegedly capable of inhibiting noxious sensation being transmitted from other areas of the body⁷⁰. Counterirritant generated chemical/thermal sensation conducted along C-polymodal nociceptors could 'close the pain gate' on impulses transmitted along other C-polymodal nociceptors and smaller A-delta fibers conducting noxious sensation from other areas of the body. Through such spinal segmental inhibitory mechanisms,

counterirritants are thought to block the transmission of pain signals from the periphery to higher centers of the nervous system⁷¹.

Supraspinal inhibitory pathways are also thought to assuage pain within the context of the counterirritation theory. Sensations produced by counterirritants are relayed to the central nervous system where it is suggested that the hypothalamus⁷², locus coeruleus, substantia nigra, hippocampus⁷³ nucleus raphe magnus, and periaqueductal gray area^{36,38} are affected. The locus coeruleus projects to the dorsal gray horn of the spinal cord, and it may receive projections from the periaqueductal gray area. The periaqueductal gray area projects through the nucleus raphe magnus and on to the dorsal gray horn. The periaqueductal gray area receives direct input from the thalamus, hypothalamus, and reticular formation; it receives indirect input from the cerebral cortex which uses the aforementioned structures to relay its signals^{36,38}. The periaqueductal gray area is also important as it is involved with the periaqueductal gray endogenous analgesia circuit^{36,38,74}. This circuit involves a relay from supraspinal centers to the second lamina of the dorsal horn of the spinal cord. In the dorsal horn, interneurons contain enkephalin are stimulated to release their contents into the bloodstream, facilitating inhibition of synaptic impulses of C-polymodal and A-delta nociceptors^{74,75}.

Several studies support the effectiveness of counterirritants. Many of these studies have tested the efficacy of camphor and capsaicin, specifically. One study

demonstrated that camphor stimulates TRPV1 receptors, though a higher concentration of camphor than capsaicin was required to do so. Although a greater concentration of camphor is required, the study found it worked more rapidly and completely than capsaicin to stimulate TRPV1 receptors⁷⁶.

Another randomized, double blind, placebo controlled study of a counterirritant cream in which camphor was used as a main ingredient investigated pain relief of osteoarthritis in the knee⁷⁷. Sixty-three patients received either the counterirritant cream or placebo over an eight week period. Findings were analyzed with the Visual Analog Scale (VAS) for pain, the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC), and the SF-36 questionnaire. Results demonstrated the counterirritant cream was effective in alleviating osteoarthritis pain in the knee, and these results were evident in as little as four weeks.

Similarly, studies also provide some support of the efficacy of capsaicin as a pain relieving counterirritant. A systematic review of studies testing topical capsaicin for the treatment of chronic pain compiled six double blind placebo controlled trials related to the analysis of neuropathic conditions and three double blind placebo controlled trials related to the analysis of musculoskeletal conditions⁷⁸. Capsaicin was considered to be effective in pain relief if patients reported pain decreases of at least 50%. Neuropathic studies demonstrated a mean treatment response rate of 57% at four weeks (range was 53% to 75% for individual trials)

when capsaicin concentration was 0.075%. The mean placebo response rate was 42% (range 31% to 55%). The mean treatment response rate at eight weeks was 60% (range 20% to 75%); the mean placebo response rate remained at 42% (range 10% to 65%). For musculoskeletal conditions, the mean treatment response rate at four weeks for capsaicin 0.025% was 38% (range 34% to 42%) while the mean placebo response rate was 25% (range 17% to 37%). This review concluded that the effectiveness of capsaicin for pain relief was moderate, at best.

Though such studies depict counterirritants like capsaicin as marginally beneficial, further analysis of these same results suggest that these substances generate significant gains for pain relief. A systematic review of the aforementioned capsaicin study proposes that counterirritants like capsaicin are only considered moderate pain relievers the thermal sensations they produce are not readily tolerated by a large percentage of test subjects. Tramer suggests that these chemicals actually provide positive results if used in conjunction with other more tolerable treatments⁷⁹ such as heating pads or hot baths. Because many patients do not prefer counterirritants as a primary treatment due to the relative discomfort they produce, Tramer suggests that these substances could be used more effectively as supplementary treatments or as first line treatments for pain.

Placebo Effect

A placebo may be characterized as a substance or procedure administered in conjunction with suggestions that it will modify a symptom or sensation, but

unknown to the recipient, has no specific influence on the disease process in question^{80,81}. The negative connotation affiliated with placebo treatments has faded away as an increasing number of placebo-related experiments have offered support of its efficacy.

Four psychological mechanisms allegedly account for placebo effects: classical conditioning^{82,83,84}, expectancy^{84,85} anxiety and stress response^{83,84} and motivation^{84,86}. The most common example of conditioning is that of Pavlov's dogs who were conditioned to associate the sound of a bell (conditioned stimulus) with that of food delivery (unconditioned stimulus). Characteristics of conditioning include memory storage of the learned association, reinforcement with repetition, generalization of the response to a wider set of triggering stimuli (stimulus substitution), and dormancy of the response with lack of reinforcement (though complete distinction is rare). Expectancy is characterized by conceptualization that a given treatment will be effective or ineffective^{84,85}, and it is facilitated through observational learning, self-learning, and verbal instruction. Anxiety and stress hypothetically generate placebo analgesia upon their reduction within the body^{83,84,87}. Anxiety and stress arouse the sympathetic nervous system and generate excessive motor activity; this heightens the experience of new pain. Motivation influences placebo treatments, drawing from the theory cognitive dissonance^{84,88}. This theory describes two or more beliefs that create conflict in an individual. To eradicate the conflict, the individual intensifies his belief in the belief he wants to be true. When a medical professional tells a patient a certain

treatment will help him and that treatment fails, dissonance is created. The patient does not want to believe the treatment has failed, so he further invests himself in the treatment, creating a placebo effect.

Placebo treatments are also distinguished by physiological factors. Excitement of the ventrolateral PAG region produces an analgesic effect which may be suppressed by naloxone, an opiate receptor blocking agent, specifically within the dorsal raphe nucleus of the brainstem^{24,26}, suggesting that the form of analgesia it generates is of an opioid form. Several studies indicate placebo related analgesia is mediated by the endogenous opioid system as this analgesia is successfully suppressed by naloxone^{84,89}, particularly where motivation is involved. These findings ostensibly verify the efficacy of placebo.

Mechanisms of analgesia are found not only in the ventrolateral PAG, but also within the cortex and subcortical structures of the brain^{84,90}. More specifically, the prefrontal cortex is involved in memory, arousal, expectation, conditioning, perception and motivation; all of these may directly or indirectly influence the ventrolateral PAG and effectively alter the pain experience^{10,25,84}. This evidence insinuates that the aforementioned psychological processes generated by placebo treatments may stimulate the areas of the ventrolateral PAG and brainstem related to the production of analgesia. The prefrontal cortex is also linked to the occipital, parietal, and temporal lobes; resultantly, it may access sensory experiences and past experiences that influence pain perception⁸⁴. Cortical and

subcortical regions, including the thalamus, hypothalamus, and amygdale of the limbic system are crucial to emotional responses, especially to those related to pain and pain relief^{10,84,91}. The placebo responses associated with conditioning and expectancy may stimulate the limbic system and excite the same analgesic centers that accessed by the periphery⁸⁴. Such analgesic response is significant because it suggests that pain may be controlled by cognition.

Studies indicate thermal modalities are capable of eliciting a placebo response from the body. One study tested the efficacy of low-level topical heat therapy by testing the effects of heat back wraps, unheated back wraps, oral ibuprofen (400 mg), and oral placebo upon a group of 76 individuals experiencing moderate to severe lower back pain⁹². Subjective measures of pain relief, muscle stiffness, trunk range of mobility, and Roland Morris disability were evaluated. After three days, an assessment of the heat wrap treatment versus heat wrap placebo treatment (unheated back wraps) displayed an efficacy of 2.75 and 1.45, respectively ($p = 0.00005$). Trunk range of motion increased 20 cm for heat wrap treatment and 17 cm for heat wrap placebo treatment ($p = 0.001$). Muscle stiffness decreased 63.7% for the heat wrap group and 52.1% for the heat wrap placebo group ($p = 0.0008$). Roland Morris disability measures marked a pain decrease of 85% within the heat wrap group and a decrease of 76% within the heat wrap placebo group ($p = 0.005$). This study shows marked gains in individuals who received only placebo treatment, and it provides credible

evidence that placebo works in conjunction with thermal modalities to alleviate pain.

Summary

The gate control theory operates via two methods to alleviate pain. First, axon collaterals of A-beta afferents synapse with axon terminals of A-delta and C-fibers. Action potentials from A-beta afferents consequently stimulate A-delta and C-fibers, eliciting the release of their neurotransmitters^{17,35}. As a result, the A-delta and C-fibers enter a refractory period in which noxious stimuli cannot excite them. This process, known as presynaptic inhibition, is one process by which the gate control theory relieves pain. The second method relates to the conduction speeds of A-beta fibers as they compare to those of A-delta and C-fibers. A-beta afferents measure 8 μm in diameter; their average conduction velocity measures 50 m/s^{6,92,93}. A-delta and C-fibers measure 3 μm and 0.5 μm , with average conduction velocities of 15 m/s and 1 m/s, respectively^{6,92,93}. The larger diameter of A-beta afferents offer increased surface area for signal conduction that permits quicker conduction speeds than the smaller A-delta and C-fibers. Resultantly, impulses carried by A-beta afferents reach the spinal cord dorsal gray horn more quickly than impulses carried by A-delta and C-fibers; these impulses are carried to the brain to be processed, consequently “closing the pain gate” on the impulses from A-delta and C-fibers⁵.

It is difficult to assess whether or not thermal stimuli trigger A-beta afferents and consequently close the pain gate on A-delta and C-fibers. A-beta afferents only respond to mechanical stimuli like touch; current research does not definitively link the efficacy of thermotherapies in pain relief to A-beta afferents and the gate control theory. Rather, it is more likely that A-delta and C-fibers interact with each other, opening and closing the pain gate by themselves. Thermal sensations reach noxious levels as they approach 45° C^{14,17,18,35}. If there were enough semi-noxious thermal stimuli, the present noxious stimulus would be overwhelmed and subsequently inhibited. Additionally, pre-synaptic inhibition¹⁹ would some degree of pain relief; the thermal stimulus would leave A-delta and C-fibers in a refractory state that reduces the amount of neurotransmitter that may be released during subsequent stimulation. This would limit the degree of pain impulse interpreted by the brain.

Descending inhibitory mechanisms utilize efferent sensory pathways; the PAG is stimulated by inflammation or injury in the periphery, and it relays analgesic messages to the dorsal horn of the spinal cord, consequently inhibiting pain signals^{20,21,22,23}. The ventrolateral column of the PAG generates an opioid form of analgesia, while the lateral column of the PAG creates non-opioid analgesia^{24,26}. The ventrolateral column utilizes serotonin, and the lateral column uses noradrenaline; the serotonergic systems respond to thermal nociceptive stimuli; the noradrenergic systems respond to mechanical nociceptive stimuli³².

Thermoreceptors respond to thermal stimuli, and as those stimuli approach 45° C, they merge with and supersede signals being carried by A-delta and C-fibers^{14,17,18,35}. These sensations travel to the ventrolateral PAG via spinothalamic pathways. The ventrolateral PAG stimulates the nucleus raphe magnus which sends signals to enkephalinergic interneurons in the substantia gelatinosa of the dorsal horn by way of serotonergic efferent fibers^{2,33}. The enkephalinergic interneurons synapse with A-delta and C-fibers, and they consequently inhibit them from responding to more pain signals by releasing an endogenous opioid, enkephalin. Semi-noxious or noxious thermal stimulation of A-delta and C-fibers are also believed to trigger the release of other endogenous opioids like beta-endorphin and dynorphin directly into the bloodstream by the anterior pituitary gland¹. Not only does the stimulation of A-delta and C-fibers leave the afferents in a refractory state, but also, the excitement of the ventrolateral PAG and nucleus raphe magnus that control release of enkephalins which further inhibit further pain signals^{34,37,38}. However, very high temperatures are necessary to generate adequate thermal stimulation to activate enough afferents to provide large-scale pain relief^{14,17,18,35}. In addition, it takes 20 – 40 minutes to elicit the release of beta-endorphins and dynorphins from the anterior pituitary into the bloodstream²; this extended period of time could cause burning or blistering of the skin, as well as damage to the A-delta and C-fibers.

Counterirritants include one or more of these main ingredients: menthol, methyl salicylate, camphor, and capsaicin. They irritate the skin, instigating a mild

inflammatory response that will deplete A-delta and C-fibers of inflammatory mediators like substance P⁴². C-fibers are the most affected by counterirritants. Unlike A-delta fibers that respond to mechanical stimuli, thermal stimuli, and limited chemical stimuli, C-fibers respond to mechanical stimuli, thermal stimuli, and chemical stimuli^{6,12,94}. Most evidence proposes that counterirritant ingredients activate thermoTRPs within the fibers that respond to them^{49,50,51}. TRPV receptors are heat stimuli responsive; TRPM and TRPA are cold stimuli responsive.

Of the four known TRPV ion channels, TRPV1 is the most significant as it is associated with the small diameter cell bodies that supply C-fibers^{49,52,53}. TRPV1 receptors are activated by thermal stimuli above bodily pain threshold of ~43°C^{49,52,53}, as well as by chemical stimuli capable of increasing membrane permeability to Na⁺ and Ca²⁺ ions⁵⁴.

Counterirritants affect the body peripherally by targeting thermoTRPs, ultimately triggering the depolarization of C-fibers and a mild inflammatory reaction responsible for eliciting the release of inflammatory substances like substance P^{16,17,35}. Substance P accounts for the burning sensation of affiliated with counterirritants⁶⁹ by stimulating TRPV1 channels, keeping them open, and consequently maintaining their transmission of thermal sensations to the brain. Essentially, substance P acts as a chemical irritant by propagating the response of the C-fibers to external chemical stimuli, even after they are withdrawn.

Presynaptic inhibition is also accountable for a portion of the pain relief generated by counterirritants. When substance P stores are depleted by chemical stimuli, the C-fibers remain in a refractory state until the stores can be replenished by the body. During this refractory period, other painful stimuli fail to depolarize the C-fibers.

Counterirritants are also thought to relieve pain at a spinal level in a manner similar to that of the gate control theory. Essentially, chemical and thermal impulses created by counterirritants are thought to inhibit noxious sensation from other parts of the body⁷⁰. Chemical/thermal sensation from specific C-fibers could 'close the pain gate' on other C-fibers and A-delta fibers, consequently blocking the conduction of pain signals to higher centers of the nervous system⁷¹. Counterirritants acting upon supraspinal inhibitory pathways may also be affective in pain relief. The sensation generated by counterirritants reach the central nervous system where they stimulate the hypothalamus, locus coeruleus, substantia nigra, hippocampus, and PAG^{36,38,72,73}. The PAG is the most instrumental center in generating descending inhibitory mechanisms as it is affiliated with the PAG endogenous analgesia circuit^{36,38,74} that relays messages from supraspinal centers to the second lamina of the dorsal horn of the spinal cord. Descending inhibitory impulses within the spinal cord stimulate interneurons to release enkephalin into the bloodstream, a process responsible for inhibition of pain impulses^{74,75}.

Placebo can also work in conjunction with thermotherapy to assuage pain. It utilizes classical conditioning, expectancy, anxiety and stress response, and motivation^{82,83,84,85,86}.

Memory storage of the learned association, reinforcement with repetition, stimuli substitution, and dormancy of response with lack of reinforcement are all traits that describe classical conditioning. Anticipation of the efficacy or ineffectiveness of a treatment portrays expectancy, and it is expressed through observational learning, self-learning, and verbal instruction. Anxiety and stress arouse the sympathetic nervous system and instigate excessive motor activity; the reduction of anxiety and stress produces a perceived placebo effect^{83,84,87}.

Motivation utilizes cognitive dissonance^{84,88} to generate placebo: motivation intensifies and individual's belief in the positive efficacy of a treatment.

Physiologically, placebo stimulates the ventrolateral PAG to produce an opiate analgesic effect in a manner similar to descending inhibitory mechanisms.

Placebo inducing stimuli ultimately excite the ventrolateral PAG which subsequently stimulates the dorsal raphe nucleus; this nucleus relays messages to the dorsal horn of the spinal cord where interneurons are stimulated to release enkephalins^{24,26}.

Cortical and subcortical structures of the brain also explain placebo^{84,90}. The prefrontal cortex is a cortical structure responsible for memory, arousal,

expectation, conditioning, perception and motivation, all of which influence the ventrolateral PAG and resultantly stimulates pain inhibition within the spinal cord^{10,25,84}. The prefrontal cortex is affiliated with the occipital, parietal, and temporal lobes, allowing it access to sensory experiences and memories that influence pain perception⁸⁴. Subcortical regions such as the thalamus, hypothalamus, and amygdale of the limbic system also access emotional responses, specifically those that access pain and pain relief^{10,84,91}. The limbic system may also be stimulated by conditioning and expectancy, resultantly exciting analgesic centers and providing subsequent pain relief⁸⁴. This implies pain may be managed successfully by cognition.

Conclusion

To successfully explain the management of pain via thermotherapy, a combination of the gate control theory, descending inhibition theory, counterirritation theory, and the placebo theory may be used. Individually, these theories present strengths and weaknesses that both support and discourage the use of thermal modalities in terms of their physiological mechanisms and their practicality in a clinical setting.

Substantial evidence supports the physiological processes that drive the gate control theory. Research and experimentation have challenged the gate control theory since its inception in 1965. Nearly 40 years later, this theory is still reinforced by the most concrete and up to date information available. Though this

evidence confirms that mechanical stimuli effectively stimulate A-beta afferents and consequently inhibit noxious impulses, no tangible evidence exists to support that thermal stimuli work in conjunction with A-beta afferents to relieve pain. At best, one might only conclude that A-delta fibers and C-fibers interfere with each other on some level to close the pain gate by themselves. Despite the successful use of gate control theory in clinical practice, the postulation that thermotherapy works in conjunction with A-beta afferents to close the pain gate is poorly reinforced.

Concrete evidence supports the value of descending inhibition theory in both physiological and clinical terms. Onset of descending inhibition may be documented by measuring levels of endogenous opioids like enkephalins, beta-endorphins, and dynorphins within interstitial space and the bloodstream. Thermotherapy has been definitively linked to stimulation of the PAG and descending inhibition centers. Therefore, elevated levels of endogenous opioids in the bloodstream may be positively linked to the application of thermotherapy. Yet, the disadvantages of the application of descending inhibition theory in a clinical setting are also clear. Heat must be applied for twenty to forty minutes to generate a response from the PAG and descending inhibition circuit. Additionally, high amounts of heat are required to stimulate a sufficient amount of A-delta or C-fibers to trigger a response. Resultantly, one must conclude that despite overwhelming physiological support, clinical modalities based on descending inhibition may not be the best form of thermal treatment.

The theory of counterirritation is also well supported by scientific evidence, though most of this evidence has been generated within the last ten years. An increasing amount of studies have verified the existence of thermoTRPs and tracked the physiological pathways they follow to elicit responses within the spinal cord and brain. Counterirritants produce peripheral effects like vasodilation, spinal segmental effects which indicate the assistance of gate control, and supraspinal and cortical effects that stimulate the descending inhibition circuit. Specifically, the peripheral and supraspinal/cortical affects are readily measurable. However, the theory of counterirritation may be considered somewhat impractical within a clinical context due to the messy application of ointments or creams, as well as the low tolerance levels of burning sensations generated by counterirritant chemicals within many patients.

Though physiological support of the placebo effect may be somewhat elusive, credible evidence exists suggesting placebos stimulate descending inhibition centers within the brain via psychological stimuli. The limbic system and amygdala are linked to the PAG. When the PAG is stimulated by a physical stimulus, the limbic system and amygdala send information concerning past experiences and memories into the PAG. The mind associates heat with relaxation and peace of mind. Thermal stimuli that excite the PAG may elicit a psychological response from the limbic system and amygdala that enhances descending inhibition mechanisms within the body. Yet, placebos are often

negatively perceived due to subjective aspect drawn out by the subjective psychological aspects. For this reason, placebo effect is not often considered to be a credible theory related to thermotherapy.

Further study is required to more accurately depict the connections between the gate control theory, descending inhibition theory, counterirritation theory, placebo affect and the physiological mechanisms that enable thermotherapies to work effectively. Evidence now suggests that one definitive resolution may not be reached. It is increasingly likely that thermotherapies work in the context of several theories to activate similar analgesic circuits. Hopefully, as science progresses, means of administering therapeutic thermal agents will advance to such a point that all of the theories might be applied together within a clinical setting, and the difficulties and obstacles accompanying each will be eliminated.

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