Published in final edited form as:
Clin J Pain. 2014 June ; 30(6): 544–555. doi:10.1097/AJP.0b013e3182a0e383.

Review of overlap between thermoregulation and pain modulation in fibromyalgia

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Abstract

Fibromyalgia syndrome is characterized by widespread pain that is exacerbated by cold and stress but relieved by warmth. We review the points along thermal and pain pathways where temperature may influence pain. We also present evidence addressing the possibility that brown adipose tissue activity is linked to the pain of fibromyalgia given that cold initiates thermogenesis in brown adipose tissue via adrenergic activity, while warmth suspends thermogenesis. Although females have a higher incidence of fibromyalgia as well as more resting thermogenesis, they are less able to recruit brown adipose tissue in response to chronic stress than males. In addition, conditions that are frequently comorbid with fibromyalgia compromise brown adipose activity making it less responsive to sympathetic stimulation. This results in lower body temperatures, lower metabolic rates, and lower circulating cortisol/corticosterone in response to stress - characteristics of fibromyalgia. In the periphery, sympathetic nerves to brown adipose also project to surrounding tissues, including tender points characterizing fibromyalgia. As a result, the musculoskeletal hyperalgesia associated with conditions like fibromyalgia may result from referred pain in the adjacent muscle and skin.

Keywords

Thermoregulation; Thermogenesis; Nociception; Adrenergic; Sympathetic; Catecholamine; Positron emission tomography; PET

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Introduction

Fibromyalgia syndrome is a chronic condition characterized by musculoskeletal pain that persists for many years and is unresponsive to anti-inflammatory and analgesic compounds.[1] In addition to decreased body temperature,[2] several characteristics of fibromyalgia syndrome suggest altered thermoregulatory activity. First, the distribution of brown adipose tissue (BAT) resembles that of tender points, anatomical locations that have been used to diagnose fibromyalgia.[1] This relationship may support referred pain in muscles similar to the referred pain of angina. Secondly, BAT activity at rest and the incidence of fibromyalgia are each relatively greater in females than males, whereas adaptive thermogenesis is greater in males than females.[3],[4] Thirdly, stress and cold each stimulate thermogenesis[5] and aggravate symptoms of fibromyalgia,[6] whereas warmth suspends thermogenesis and temporarily relieves the symptoms of fibromyalgia. Fourth, regulation of thermogenesis and pain share several areas in the brain where they may influence each other. Fifth, injections of a local anesthetic into stellate ganglia (sympathetic projections to subclavicular BAT) reduce pain in patients with fibromyalgia.[7] Sixth, extended programs of exercise relieve symptoms of fibromyalgia, improve thermoregulation,[8–10] decrease adrenergic activity, and inhibit recruitment of BAT. Based on these associations, we examine here the possible overlap between thermoregulation and the modulation of nociception that are consistent with the symptoms of fibromyalgia.

We include information from studies that address the overlap in circuitry of thermoregulatory and pain pathways with a focus on how these topics may relate to our current knowledge of the biological characteristics of fibromyalgia. The result is a literature review that is not intended to be comprehensive as excellent reviews of thermoregulation and of fibromylaglia already exist. Instead, this review highlights multiple areas that warrant additional study to delineate the nature of the relationship between fibromyalgia and thermoregulation.

Fibromyalgia syndrome

After exclusion of other painful disorders, the widespread pain of fibromyalgia is characterized by pain in spite of an absence of gross pathology at these or the surrounding large areas of hyperalgesia. While newer diagnostic criteria are proposed,[10] the sensitivity and number of tender points out of 18 specific anatomical locations (Figure 1A) remain a useful investigative tool. These 18 points are distributed symmetrically on the trunk and proximal regions of limbs rather than areas that are usually more sensitive to tactile stimulation in healthy individuals, such as hands, feet, genitals, and mouth.[11],[12] Pain is not restricted to tender points; rather, the location of tender points was selected based upon their relative insensitivity to palpation in healthy normal controls. In contrast, only slight pressure at these sites often induces pain in patients with fibromyalgia. Hormones may be important as fibromyalgia is more common in women than in men, and pain sensitivity in healthy women varies over the menstrual cycle.[13]

Patients with fibromyalgia often report physical or emotional trauma prior to the onset of their condition,[14] and stress exacerbates their symptoms. Patients are plagued by non-

restorative sleep,[15,16] fatigue,[1] cold intolerance,[17] and neuroendocrine abnormalities[11] including abnormally high heart rate, low metabolic rate, low body temperature, and decreased temperature and vasoconstriction in skin over tender points.[2] There is also a high prevalence of obesity,[18,19] insulin resistance,[20] and hyperlipidemia.[20] Their pain appears sensitive to sympatholytic maneuvers and rekindles upon injection with norepinephrine.[21] Except in a single study,[22]polymorphisms in catechol-O-methyl transferase have been linked to fibromyalgia,[23–27] raising the possibility that faulty degradation of catecholamines increases the risk of developing fibromyalgia.

In healthy individuals, acute stress can either increase or decrease pain perception, depending on how stress affects various secreted proteins and their receptors. In patients with fibromyalgia syndrome, minor daily stresses, particularly cold stress, frequently exacerbate the symptoms of fibromyalgia. Conditioned pain modulation [CPM, previously called diffuse noxious inhibitory controls (DNIC)] can be measured in humans to assess pain sensitivity after immersion of their arms in hot (47°C)[28] or cold (12°C)[6] water. Healthy individuals perceive pain more in ascending trials when progressively greater areas of the arm are dipped into water, than when the whole arm is initially immersed and thereafter incrementally less surface area exposed. This suggests recruitment of inhibitory systems by immersion of the whole arm. That fibromyalgia patients fail to perceive this difference between the two types of exposure suggests a deficit of endogenous pain inhibitory activity.[29,30] After the arm is withdrawn, pain induced by the cold water persists longer in fibromyalgia patients than in controls.

In cerebrospinal fluid from patients with fibromyalgia, there is an increased concentration of substance P,[31,32] dynorphin,[33] and nerve growth factor (NGF).[34] In the serum, brain-derived neurotrophic factor (BDNF), the trophic factor that establishes mechanosensitivity of sensory nerves in the adult, is elevated.[35] There is no obvious tissue damage in areas of the body that are reported as painful.[36] Although peripheral defects have been identified,[37] fibromyalgia is primarily attributed to hypersensitized pain pathways in the brain or spinal cord.[38] Yet none of the proposed central or peripheral defects explains the unique distribution of mechanical hypersensitivity, i.e. in and near the trunk, characteristic of fibromyalgia pain.

While stress increases the severity of their symptoms,[39–43] patients' hypothalamic-pituitary-adrenal (HPA) responses to stress are attenuated.[44] In contrast, their resting adrenergic activity remains high[45] resulting in a diminished heart rate variability, especially at night.[45] Corticotropin-releasing factor (CRF) together with enhanced sympathetic tone[45] may underpin the characteristic sleep disturbances and elevated heart rate in these patients. Others report reduced epinephrine responses to hypoglycemia,[44] yet an intravenous injection of interleukin-6 in patients with fibromyalgia dramatically increases norepinephrine more than in healthy controls.[46]

There is a high comorbidity between fibromyalgia and other painful or inflammatory disorders. For example, patients with fibromyalgia have a higher incidence of ulcerative colitis (19%),[47] irritable bowel syndrome (about 70%),[48–51] interstitial cystitis,[52,53] vulvodynia,[54] migraines (35.6%),[55] Sjögren's syndrome,[56] and endometriosis[57] than general

female populations. The incidence of fibromyalgia in people with Crohn's disease is reported to be as high as 49%[47] or as low as 3%.[58] These comorbidities may be due to similar etiologies, as previously proposed for migraine and fibromyalgia.[59] Alternatively, they may result from viscerosomatic convergence on second order dorsal horn neurons in the spinal cord[60] and thalamic neurons[61,62] allowing somatic afferent activity to influence visceral sensations, and vice versa.[63] This hypothesis, however, does not explain why patients with inflammatory disorders do not all develop fibromyalgia.

Exercise alleviates fibromyalgia, improving a variety of its symptoms. Even in healthy individuals aerobic exercise decreases blood pressure,[64] lowers resting heart rate,[65] increases heart rate variability,[66] increases vagal tone,[67] and decreases sympathetic tone.[68] Individuals who regularly exercise have increased basal metabolic rates,[69] lower white adipose tissue,[70] greater baseline cortisol concentrations, and an increased response to stress-induced release of cortisol.[71] Moreover, regular exercise improves sleep patterns,[72] and lessens physical and mental fatigue.[73] It improves circulation to muscles, skin and organs[67,74] and lowers the risk of obesity or diabetes by improving the regulation of insulin and blood glucose.[75] Exercise not only increases bowel motility in normal individuals,[76] it improves symptoms associated with irritable bowel syndrome,[77] a condition frequently diagnosed in patients with fibromyalgia.

Brown adipose tissue (BAT)

BAT is distributed in areas of the body that maintain body temperature in the face of cold exposure by a process referred to as nonexercise thermogenesis.[78,79] In addition to its characteristic distribution, primarily in interscapular (rodents) or supraclavicular (humans) depots, it can also be found in the supra axial and perirenal areas; in striations of skeletal muscle; between the skin and underlying muscle; and on top of sympathetic ganglia (Figure 1B). BAT does not store fat and glucose but uses them to generate heat. Vascular convection carries this heat to adjacent vital organs, such as the thoracocervical regions of the spinal cord, heart, and other thoracic organs. BAT undergoes 'recruitment' (increased mass) in response to repeated cold, diets chronically high in calories, or repeated stress. Cross-adaptation between cold and stress (e.g., immobilization of rats) enhances thermogenesis,[5] whereas increasing age in rats[80] and corticosteroid administration in mice[81,82] reduce thermogenic activity and thermal capacity of BAT.

Although non-shivering thermogenesis induced by cold and stress prevails in many nonhuman primates, it was previously thought inactive in human adults. However, residual BAT remains in most humans.[83] When active, BAT takes up ^{18}F-fluorodeoxyglucose and is visible in and interferes with positron emission tomography (PET), motivating practices that decrease thermogenesis during routine scans. Visualization of BAT on PET scans is decreased by a high fat, very-low-carbohydrate, protein-permitted diet for 5 hr before scans at a normal room temperature[84] by suppressing glucose metabolism.[85] Though found primarily in cervical-supraclavicular depots, BAT is widely distributed, but few PET scans taken at 22°C (72°F) reveal BAT when analyzed retrospectively (only 7.5% of women and 3.1% of men),[86] likely due to fasting prior to scans. Other PET studies report higher percentages, ranging from 25% of patients with visible BAT[87] to more than 80%[88] when

taken at room temperature. One autopsy series identified BAT in the necks of 84% of patients over the age of 20,[83] indicating that this tissue is generally retained into adulthood. Consistent with this, BAT is readily apparent in PET scans in men exposed to 16°C (61°F) cold temperatures prior to their scan.[89]

Thermogenesis is initiated by enhanced sympathetic activity to BAT.[90] Norepinephrine turnover is higher in cold-acclimated rats than in rats kept at thermoneutrality, reflecting a high sympathetic tone under cold conditions. The released norepinephrine acts at α_2- and β_3-adrenergic receptors, causing production of heat in areas surrounding vasculature leading to vital organs. While β-adrenergic receptors increase thermogenesis and adenosine 3′,5′-cyclic monophosphate (cAMP) production in humans, α_{2A}-receptors decrease them,[91] such that the balance between α_2- and β_3-receptor activity is key. Cold, stress, or overfeeding initiate sympathetic activity, increasing release of norepinephrine and β-adrenergic activity. Chronically, they increase lipolysis; raise thermogenic activity; induce uncoupling protein (UCP) expression; and recruit BAT. After cold adaptation in hamsters, although the noradrenergic system is tonically activated, the sensitivity of BAT to norepinephrine decreases due to down-regulation of adrenergic receptors,[92–94] especially β_3-receptors in rats,[95] and G_s-protein,[96] limiting adrenergic activity.

Thermogenic activity contributes to metabolic activity, temperature regulation, and regulation of body weight. During thermogenesis, adrenergic stimulation of lipolysis in BAT produces fatty acids that are channeled into the mitochondrial β-oxidation pathway. Lipid oxidation in turn leads to increased NADH and $FADH_2$ production and electron transport chain-dependent proton pumping producing an increased proton gradient across mitochondrial inner membranes. Such a gradient is dissipated by ATPase or by uncoupling proteins (UCPs) that facilitate proton leak and heat production. Although several UCPs have been identified, only UCP1, found in BAT, takes part in thermogenesis. UCP2 is distributed in many tissues, including the brain and primary afferent fibers,[97] areas involved in temperature regulation whereas UCP3 is localized in skeletal and cardiac muscle.

The likelihood of having substantial BAT activity at rest is threefold greater in women than in men, indicating a greater resting thermogenesis in females. The greater mass of BAT and greater percent of their body devoted to BAT suggest that women have a high thermogenic capacity as well as activity.[86] Physiologic concentrations of female sex hormones promote, while testosterone inhibits, thermogenesis. While ovarectomy decreases UCP1 in BAT,[98] estrogen increases BAT fat pads and oxygen consumption in rats.[99] Estrogen and progesterone each increase β_3-adrenergic receptors, while there are lower levels of inhibitory α_{2A}-adrenergic receptors in female than in male rats.[4] This higher ratio of β_3- to α_2-receptors may be key to the higher basal thermogenic capacity and resting expression of UCP1 in females.

Gender influences the recruitment of BAT in rats in response to chronic cold[100] and chronic overfeeding.[101] There is a greater thermogenic capacity and a lesser body weight gain in males than in females after chronic feeding, chronic cold or chronic stress. This suggests “induced” thermogenic activity is lower in females than in males. High concentrations of estrogen inhibit cold-induced thermogenesis in rats[102] in spite of similar sympathetic

activity (norepinephrine turnover) across sexes during cold acclimation.[103] There is a preferential recruitment of β3-receptors by norepinephrine, resulting in higher levels of β_3-adrenergic receptors in male than in female rats. In chronic situations, the high ratio of β_3- to α_{2A}-activity in males likely sustains their greater thermogenic capacity in rats[3] and recruitment of BAT in mice.[104]

An important therapeutic intervention in patients with fibromyalgia is a sustained pattern of gradually increased daily exercise. Acutely, physical activity generates heat in skeletal muscle and inhibits thermogenesis in BAT. However, the effect of chronic exercise training on BAT is unclear. In mice, BAT activity and mass were unchanged by swim-training,[105] whereas more frequent daily swims increased the mass of BAT in mice.[106] In Wistar-Shizouka Takagi rats, intermittent training produced no change in BAT activity (treadmill),[107] while more continuous training programs decreased BAT mass in Wistar rats (treadmill)[108] and Sprague-Dawley rats (swimming).[109] To resolve these conflicting results, de Castro and Hill[110] speculated that exercise can be a stressor, and thereby increase sympathetic activity to BAT. Using voluntary running of rats, their results were consistent with those in humans indicating that as physical activity increases, the metabolic activity of BAT also increases, generally improving thermoregulation.[9],[111] At temperatures that normally induce recruitment in rats, chronic exercise eliminates the recruiting effect of cold.[112–114] In summary, exercise prevents recruitment of BAT.

Association of BAT with fibromyalgia

Basal thermogenic activity and a predisposition to having fibromyalgia are greater in females than in males. Thermogenic activity is increased by the same conditions that exacerbate the symptoms of fibromyalgia, i.e. cold and mild daily stress. In contrast, thermogenic activity and symptoms of fibromyalgia are minimized by warmth and by gradually increasing daily exercise. Yet patients generally have sluggish rather than stimulated rates of metabolism. Lower than anticipated thermogenic responses to cold mimic the tendency for these patients to have relatively low basal concentrations of circulating cortisol and attenuated cortisol responses to stress in spite of excessive activation of the HPA axis.[41] The following summarize thermoregulatory and nociceptive processing (Table 1) that may overlap, supporting abnormal responses in patients with fibromyalgia to stress and cold.

Innervation of BAT and surrounding tissues

Although the pain of fibromyalgia is widespread, tender points have been traditionally tested in the diagnosis of fibromyalgia. Tender points have greater sensitivity to pain upon palpation in fibromyalgia patients compared to healthy controls. In humans, nerves projecting to BAT are located near regions surrounding tender points, primarily in the supraclavicular region, but also in supra axial, perirenal and subcutaneous areas. This anatomical overlap may provide collateral innervation of tissue adjacent to BAT, e.g., skin and muscle, by sympathetic and primary afferent nerves. Consistent with this, when BAT is activated by injections of adrenaline in rats, muscles surrounding interscapular BAT have greater blood flow than in muscles of the anterior limbs,[115] indicating that adjacent tissues

operate in synergy with BAT. Consistent with increased adrenergic tone to these areas, the temperature is lower in the skin above tender points,[2] suggesting that vasoconstriction and local hypoxia in skin coincides with vasodilation in muscle, as shown schematically in figure 2. Consistent with a possible simultaneous activation of BAT and skeletal muscle, UCP1 mRNA is detected in progenitor cells in human skeletal muscle and its expression is increased in vivo by PPARγ agonist treatment.[116] As a result, sympathetic activity that induces thermogenesis is poised to induce hyperalgesia in tissues surrounding BAT by referred pain. Angina is a good example of referred pain perceived in non-cardiac structures as well as the heart.[117] The pain of angina overlaps unilaterally with some tender points associated with fibromyalgia consistent with their common innervation via stellate ganglia.

Sympathetically-maintained pain

That sympathetically-maintained hyperalgesia[118] contributes to pain in patients with fibromyalgia is evidenced by the ability of norepinephrine to cause pain in these patients.[21] Consistent with this, local anesthetics applied to stellate sympathetic ganglia[7] innervating BAT produces analgesia in patients with fibromyalgia. This suggests sensitization of adrenergic receptors or a failure of these sites to desensitize as they usually do in rats.[92–94] Adrenergic receptors are upregulated and pronociceptive after sympathectomy, as shown by enhanced nociception produced by norepinephrine after removal of the superior cervical ganglion in rats.[119] Hyperalgesia can also be mediated by α_2-adrenergic receptors on postganglionic sympathetic nerves, such as after application of chloroform to rat paws,[120] or by increased expression of α_2-adrenergic receptors on primary afferent fibers,[121] such as in rabbits after tissue injury.[121,122] Capsaicin-sensitive thermal hyperalgesia in the rat depends on α_1-adrenergic receptors on primary afferent C-fibers[123] whereas mechanical hyperalgesia elicited by epinephrine injected intradermally in rats results from activation of G-protein-coupled β_2-adrenergic receptors on primary afferent fibers.[124] Large-diameter axotomized sensory neurons can be activated by sympathetic stimulation when nerve injury causes basket-like structures to sprout from sympathetic nerves within dorsal root ganglia of rats,[125] a hyperalgesic condition relieved rather than caused by sympathectomy.[126]

Primary afferent fibers

After adrenergic fibers activate BAT, primary afferent C-fibers detect heat generated[127] and feedback to inhibit BAT activity by releasing calcitonin gene-related peptide (CGRP) peripherally and centrally.[128] Paradoxically, during chronic cold, primary afferent C-fiber activity is needed to recruit BAT by adaptive thermogenesis (i.e. increased UCP1 synthesis and enhanced mass) as desensitization of these afferents prevents recruitment.[129] Sensitized primary afferent C-fibers projecting to BAT discharge at lower temperatures, enhancing feedback inhibition of thermogenesis (causing hypothermia) and simultaneously causing hyperalgesia in adjacent skin and muscle that is innervated by these sensitized collaterals. Based on the high pain sensitivity at tender points near areas of BAT together with abnormally low body temperature, the symptoms of fibromyalgia may result from sensitized primary afferent C-fibers innervating BAT and adjacent tissues[128] causing referred pain. Patients with fibromyalgia may respond abnormally to cold and stress as conditions that are frequently comorbid with fibromyalgia inhibit adaptive thermogenesis.

Sensitization

Sensitization of primary afferent C-fibers may occur due to activation of capsaicin-sensitive, transient receptor potential vanilloid (TRPV1) receptors on nociceptors and on temperature-sensing afferents. TRPV1 antagonists induce hyperthermia in rat[130] indicating these receptors remain tonically active in mammals to protect against hot temperatures causing tissue damage. This tone is provided by oxidized linoleic acid metabolites (OLAMs), such as 9- and 13-HODE acids. OLAMs activate TRPV1 sites on nociceptors causing hyperalgesia[131,132] and elicit a sensation of warmth but decrease body temperature.[133] Low doses of TRPV1 agonists enhance pain,[133,134] but high doses desensitize TRPV1 sites. OLAMs are also ligands of PPARγ receptors whose activity is necessary for adaptive thermogenesis.[135] By altering concentrations of 9- or 13-HODE, chronic defeat stress in rodents not only causes hyperthermia[136] and increases UCP1 mRNA,[137] it also increases thermal[138,139] and mechanical hyperalgesia.[140] Chronic inflammation also increases expression of TRPV1 receptors.[141] which could account for both the lower body temperature and mechanical hyperalgesia in fibromyalgia patients as various inflammatory conditions are frequently comorbid with fibromyalgia. Capsaicin-induced hyperalgesia even correlates with overall pain scores in these patients.[142]

Substance P

Substance P, released from primary afferent C-fibers transmitting pain or temperature, causes vasodilation in skin to dissipate heat and induces hyperalgesia. Centrally, substance P sensitizes nociceptive pathways and initiates cooling behaviors.[133,143] Although the high concentration of substance P in the cerebrospinal fluid of patients with fibromyalgia has been postulated to originate from nociceptive fibers, it may originate instead from temperature-sensitive fibers. Regardless of its origin, elevated substance P may account for lower body temperatures and hyperalgesia in patients with fibromyalgia. One model of fibromyalgia based on repeated exposures of rodents to cold[144] depends on spinal substance P activity for hyperalgesia.[145] If substance P decreases body temperature below normal, this may trigger thermogenic activity, enhancing sympathetic tone to BAT. Thus pain may result from the combined effect of substance P along nociceptive pathways together with sympathetically-mediated hyperalgesia in skin and muscle surrounding BAT, similar to the pain of angina.[117]

Nerve growth factor (NGF)

NGF, elevated in the cerebrospinal fluid of patients with fibromyalgia,[34] produces thermal and mechanical hyperalgesia in rodents[146,147] and humans when injected centrally[148] or peripherally into muscle.[149] Sympathetic nerves and primary afferent C-fibers each depend on NGF in target tissues for survival and specialization.[150] There is competition between adrenergic- and primary afferent C-fibers for NGF in tissues where both exist. Normally NGF originates from target tissues and is transported retrogradely to dorsal root ganglia where it regulates protein synthesis (e.g. substance P and CGRP),[150] including TRPV1 receptors.[151] Destruction of one fiber type increases availability of NGF to remaining fibers. For example, postganglionic sympathectomy increases CGRP and substance P[152] due to

enhanced NGF along nociceptors in rat.[153] Sympathectomy increases[154] while sympathetic activity decreases NGF synthesis in rats and mice.[155,156] NGF in mice causes aberrant growth of peripheral ganglia as well as abnormal sympathetic innervation of sensory ganglia[157,158] together with hyperalgesia. In summary, NGF might contribute to the hyperalgesia of fibromyalgia by increasing substance P or TRPV1 receptors and/or by promoting sympathetic tone.[31,32]

Subcortical areas

Of nuclei involved in thermoregulation,[159] the parabrachial, raphe pallidus (RP), and dorsomedial hypothalamus (DMH) are also involved in nociception.[160,161] This convergence may allow thermoregulatory signals to influence nociception. Disinhibition of the DMH activates rostroventral medulla (RVM) ON-cells and suppresses RVM OFF-cell firing causing hyperalgesia in rats.[162] Blocking serotonergic ON-cell activity prevents hyperalgesia, but does not interfere with thermogenesis, suggesting differentiation of autonomic and nociceptive transmission. Non-serotonergic ON-cells facilitate nociception but inhibit BAT activity whereas OFF-cells suppress nociceptive transmission[163,164] and potentiate BAT activity in rat.[165] Although pain and opioids each influence thermogenesis,[165] it is not known whether thermogenesis influences pain such that ON-cells, activated by thermogenesis, potentiate nociception as well as inhibit thermogenic activity. Opioid receptors contribute to antinociception by acting as are pattern generators in RVM raphe nuclei,[166] where mu opioid agonists decrease ON-cell activity and increase OFF-cell activity.[167–170] In contrast, kappa opioid agonists increase nociception in rats by suppressing OFF-cells.[171] Repeated cold exposure in mice, similar to that modeling fibromyalgia,[144] increases the pronociceptive effect of kappa opioids[172] and decreases the antinociceptive effect of mu opioid receptors, which are also down-regulated in fibromyalgia.[173]

Thermoregulatory and nociceptive pathways also converge at the parabrachial nucleus receiving somatosensory signals from spinothalamic and trigeminothalamic lamina I neurons in the rat.[174,175] Rat lamina I neurons[160] project specifically to parabrachial neurons responding to cooling[176] and to noxious stimuli,[177] as well as to polymodal nociceptive cells responding to noxious mechanical heat and cold stimuli.[178] Whereas some neurons respond primarily to cool signals from skin,[179] the majority of parabrachial neurons respond to both tactile and visceral and/or temperature input.[180] Following chronic cold or stress, thermoregulatory and nociceptive signals activate common sites, as indicated by c-fos labeling in rats,[181] increasing the role of parabrachial neurons in situations that recruit BAT. The parabrachial nucleus is a major relay for visceral inputs from the nucleus tractus solitarius to the forebrain.[182] This raises the possibility that parabrachial neurons transmit the visceral nociceptive input of abdominal disorders (like irritable bowel syndrome and interstitial cystitis that are common in fibromyalgia) to widespread nociceptive areas.

Cortical Integrators

Cortical areas implicated in fibromyalgia include the insula, amygdala, ventromedial prefrontal cortex (VMPFC), and anterior cingulate cortex (ACC) (Figure 2). They are

frequently referred to in aggregate as limbic/paralimbic cortex; they activate in response to many emotions or when affective processing is required. These regions are involved in the processing of thermal and nociceptive information, perhaps influencing their affective quality. At least some components of these networks appear dysfunctional in fibromyalgia.

The insula is the principal cortical convergence zone for the processing of internal signals that monitor the body's physiological state (e.g., pH, visceral pressures and motility, heart rate, body temperature).[183] The insula, also described as interoceptive cortex, modulates conditions within the body. For example, the human insula activates in response to visceral pain,[184,185] and insular infarcts can cause severe hypothermia.[186] Decreased metabolism of the insula occurs in healthy subjects who have detectable BAT and are exposed to environmental heat.[187] Insular activity also correlates inversely with the thermal response during hot flashes induced by adjuvant endocrine therapies[188] and plays a critical role in thermal responses to emotional processing. Human thermosensory cortex lies in the dorsal margin of the middle/posterior insula[189] and activity in the posterior insula participates in processing abnormal somatosensory feedback in fibromyalgia,[190] similar to its role in monkeys.[191] Together, the anterior insula and amygdala play a prominent role in anxiety and stress,[192–194] activating in response to aversive sensory stimuli.[162,195–197]

The ACC also participates in pain and temperature processing. Pressure on the thumb at levels that only activate somatosensory cortex in healthy controls also activate the ACC in patients with fibromyalgia.[198] The VMPFC further connects the ACC, amygdala, and insula to integrate internal signals.[199] Dysfunctional processing of such information is a component of fibromyalgia. For example, the VMPFC monitors internal milieu and is activated by introspection, by self-referential processing[200] and by the default mode state.[201] Angina arising from cardiac ischemia activates the VMPFC.[202] Even self-monitoring one's heart rate in the absence of angina activates the VMPFC.[203] The VMPFC is the origin of galvanic skin responses, reflecting a component of somatic markers involved in decision-making.[203] Lesions of the VMPFC impair decision-making, reflecting dysfunctional processing of somatic markers.[204,205] The VMPFC plays a role in sickness-related mood changes reflecting a possible overlap between fibromyalgia and depressive symptoms.[206] Fibromyalgia patients have reduced grey matter in the VMPFC and amygdala[207] similar to that in patients with chronic pain.[208] Such structural abnormalities can result from chronic abnormal metabolic activity perhaps through excitotoxic mechanisms.[209] Fibromyalgia patients differ from controls in affective processing (acoustic startle eyeblink reflex) mediated by the amygdala.[210] The VMPFC is also anatomically connected to the lateral and medial hypothalamus and periaqueductal grey,[199] making it a prime crossroad for mediating not only arousal and mood, but also pain and thermal regulation. Emotional arousal is associated with facial thermal signatures indicating an overlap between emotion and thermal regulation. Skin temperature variation in humans is associated with changes in activity within the insula, ACC, and VMPFC.[211]

Together these studies demonstrate a convergence of pain and temperature information upon central brain systems including the insula, amygdala, VMPFC, and ACC. These limbic and paralimbic structures are associated with emotion and may color the affective components of pain and sensory processing. Fibromyalgia appears to involve many of these regions.

Conclusions

This review summarizes the literature describing commonalities between the regulation of pain and temperature that may contribute to the widespread pain of fibromyalgia. Both fibromyalgia and thermoregulation are exquisitely sensitive to stress. Acute cold and stress increase the generation of heat by increasing UCP1 activity in BAT while chronically high sympathetic tone increases the synthesis of UCP1, increasing BAT volume (adaptive thermogenesis) to guard against persistent stress. The high sympathetic tone in patients with fibromyalgia aggravates their pain and should initiate adaptive thermogenesis, yet their temperature is lower than healthy individuals. This indicates either insufficient heat production or enhanced heat loss, the latter being unlikely as sympathetic tone tends to curb heat loss. Multiple points along pain and thermoregulatory pathways exist where they may influence each other. In the periphery, warmth and pain are both detected by primary afferent C-fibers that release substance P into the spinal cord, causing hyperalgesia, cooling behaviors and inhibition of BAT activity. In the brain, pain and temperature are regulated by overlapping pathways in subcortical and cortical areas. It is doubtful that body temperature alone influences nociception. Rather, the challenge of maintaining normal body temperatures in the face of acute cold or of initiating adaptive thermogenesis in response to chronic stress may be compromised by conditions that are comorbid with fibromyalgia. For example, inflammatory conditions inhibit the response of BAT to sympathetic stimulation while conditions that sensitize primary afferent C-fibers may prematurely terminate thermogenic activity by enhanced feedback inhibition of BAT, consistent with the lower body temperatures in patients with fibromyalgia. Women may be more susceptible to fibromyalgia because they are inherently less able to initiate adaptive thermogenesis than men. Insufficient activation of BAT may lead to even greater sympathetic tone, compounding the possibility of referred pain via collateral nerves projecting to areas surrounding BAT. Exercise may relieve symptoms of fibromyalgia and improve thermoregulation by gradually decreasing adrenergic activity and providing an alternate source of body heat.

Acknowledgments

The PET scan displayed was generously provided to us by Dr. Wouter D. van Marken Lichtenbelt. We extend special thanks to Ms. Allison Leuin, Drs. I. Jon Russell, Katalin J. Kovács, Tina Clarkson, Barbara Segal, and David Bernlohr for their input and helpful editorial comments on this manuscript. The authors declare no conflict of interest with any institution or company.

Support

AAL is supported by an NIH grant (AT056092) from the National Institutes on Arthritis and Musculoskeletal and Skin Diseases and by a grant from the University of Minnesota Graduate School. JVP is supported by the National Alliance for Research in Schizophrenia and Depression (NARSAD) and the Department of Veterans Affairs USA. JDP is supported by an NIH Institutional Research and Academic Career Development Award (IRACDA) grant (5K12GM074628) from the National Institute of General Medical Sciences.

Abbreviations

ACC	anterior cingulate cortex
BAT	brown adipose tissue

BDNF	brain-derived neurotrophic factor
CGRP	calcitonin gene-related peptide
CRF	corticotropin-releasing factor
DMH	dorsomedial hypothalamus
FMS	fibromyalgia syndrome
MPO	medial preoptic subregion
9-HODE	(9*S*,10*E*,12*Z*)-9-hydroperoxy-10,12-octadecadienoic
13-HODE	(13*S*,9*Z*,10*E*)-13-hydroperoxy-9,11-octadecadienoic
NGF	nerve growth factor
NT3	neurotrophin-3
NTS	nucleus tractus solitarius
PVN	paraventricular nucleus
PET	positron emission tomography
POA	preoptic area
RP	raphe pallidus
TRP	transient receptor potential cation channel
TRPV1	TR vanilloid receptor-1 or TR potential cation channel subfamily V member-1
UCP	uncoupling protein
VMPFC	ventromedial prefrontal cortex

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Significance

This review summarizes multiple intersections between the regulation of nociception and temperature that may be relevant to fibromyalgia syndrome. The working hypotheses raised may contribute to the elucidation of the etiology of fibromyalgia.

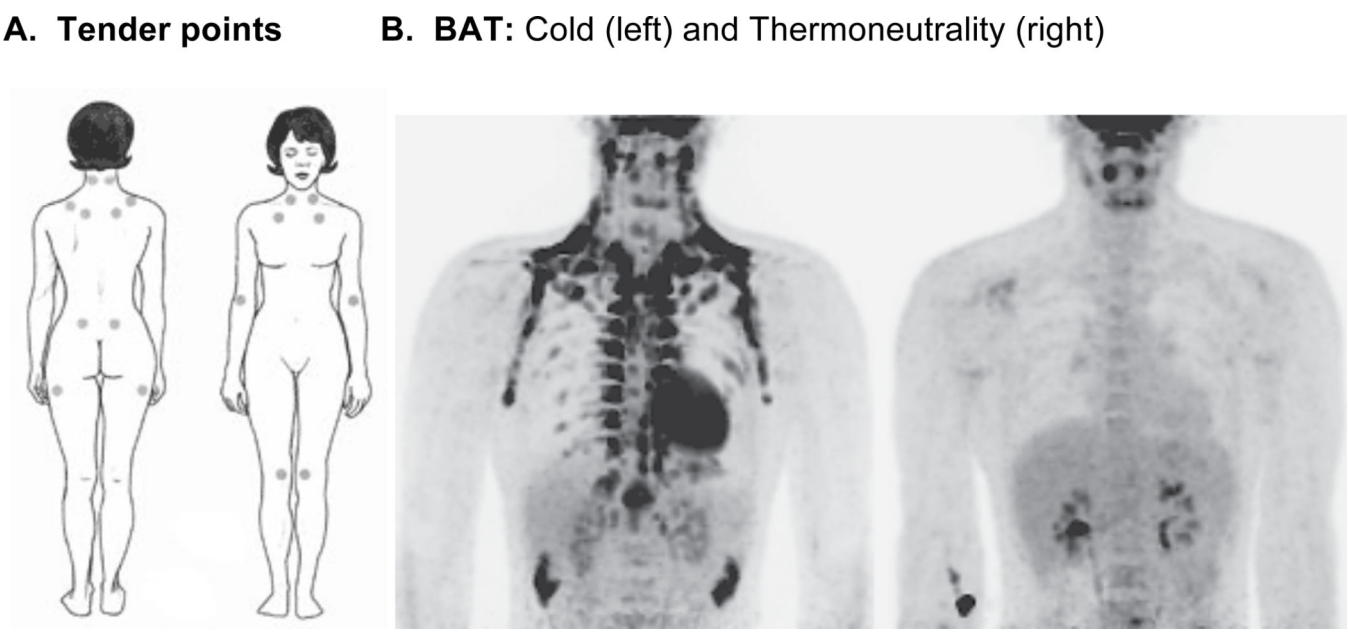

Figure 1.

Comparison between the location of tender points and BAT depots in humans. Panel A shows the location of the 18 tender points, located symmetrically, used to characterize the pain of fibromyalgia (http://www.niams.nih.gov/Health_Info/Fibromyalgia/default.asp). Panel B shows the PET scan of an individual taken during exposure to cold (left panel of figure 1B), when BAT tissue is active and visible, compared to when exposed to thermoneutral conditions (right panel of figure 1B) (from Lichtenbelt, Vanhommerig, Smulders, Drossaerts, Kemerink, Bouvy, Schrauwen and Teule).[89]

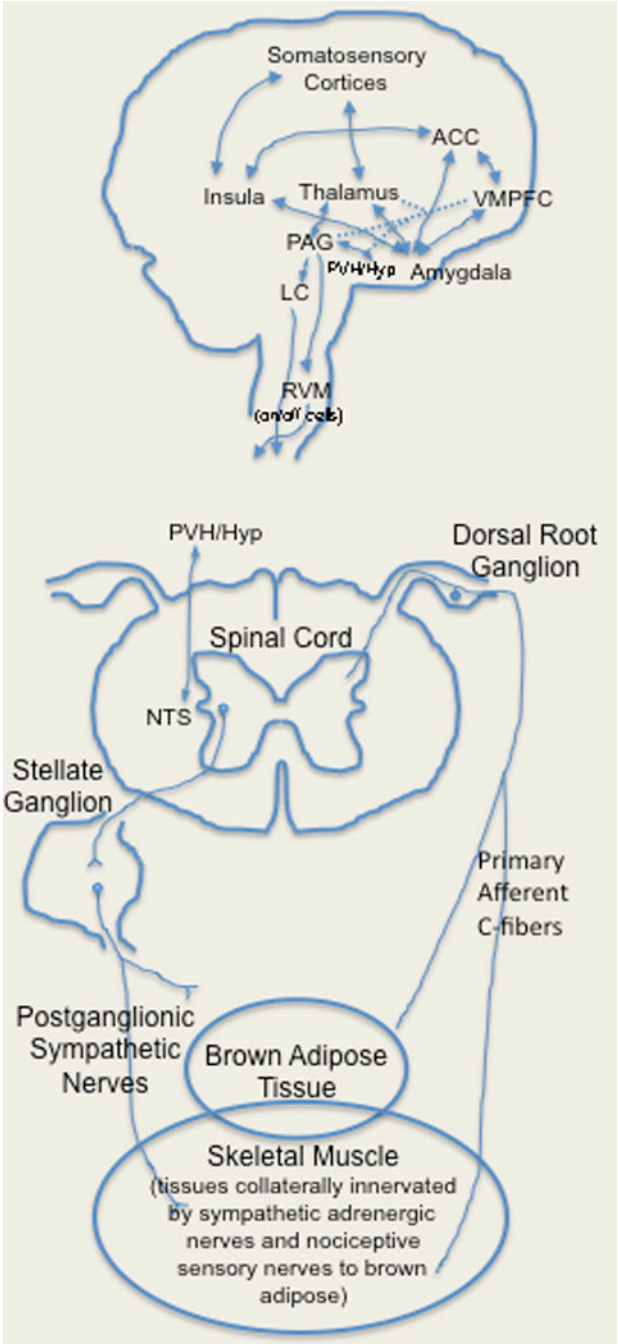

Figure 2.

Activation of brown adipose tissue may support referred pain in a fashion similar to that during attacks of angina or during the processing of other internal signals (interoception). Schematic diagram of the possible circuitry linking brown adipose tissue to surrounding muscle and skin via collateral projections of sympathetic and primary afferent C-fibers. Visceral afferent information also projects upward in the neuraxis to the nucleus tractus solitarius (NTS) and paraventricular hypothalamus (PVH). In turn, the NTS projects to the PVH, central nucleus of the amygdala, PB, and the bed nucleus of the stria terminalis (BSST). The PVH has reciprocal connections with periaqueducal grey (PAG) and amygdala. The latter directly and indirectly modulates paralimbic cortices such as the ventromedial prefrontal cortex (VMPFC), anterior cingulate cortex (ACC) and insula

thereby processing the emotional responses to pain and temperature proposed to be dysfunctional in fibromyalgia. In turn, the VMPFC has efferent modulatory projections to the PAG, hypothalamus (Hyp), and amygdala. Descending inhibitory control is exerted by the periaqueductal gray (PAG) and locus coeruleus (LC) via the rostroventral medulla (RVM) where ‘on’ and ‘off’ cells differentially modulate nociceptive signals entering at the spinal cord level.

Table 1

Substrate	Thermoregulation	Nociception
Sympathetic nerve	Activates BAT Dilates blood vessels in muscle	Constricts vessels in skin Sensitizes primary afferents to pain
Primary afferent C-fibers	Detects heat in BAT Inhibits thermogenesis Detects heat in muscle and skin	Detects pain in muscle and skin
TRPV1 receptors	Thermodetectors	Sensitize nociceptors
Substance P	Dilates vesssels in periphery Initiates cooling centrally	Sensitizes C-fibers directly Sensitizes indirectly (mast cells)
Nerve growth factor	Supports sympathetic fibers (BAT)	Supports primary afferent C-fibers Increases substance P, TRPV1, etc
Subcortical areas		
Parabrachial nucleus:	Receives temperature input	Receives tactile & visceral input
DMH:	On-cells inhibit BAT activity	On-cells support hyperalgesia
Cortical areas		
Insula:	Associated with skin temperature variation	Abnormal somesthesis in FMS Autonomic & visceral pain
VMPFC:	Crossroad for temperature Integrates interoceptive information Activated by self-referential processing e.g., angina activates	Crossroad for pain Reduced gray matter in FMS
Amygdala:	Signatures of emotion/thermal regulation Stress responses (e.g. sweating)	Reduced grey matter in FMS

Abbreviations: BAT, Brown adipose tissue; DMH, dorsomedial hypothalamus; FMS, fibromyaglia syndrome; TRP, transient receptor potential cation channel; TRPV1, TR vanilloid receptor-1 or TR potential cation channel subfamily V member-1; VMPFC, ventromedial prefrontal cortex