Phillip J. Albrecht* and Frank L. Rice

Fibromyalgia syndrome pathology and environmental influences on afflictions with medically unexplained symptoms

DOI 10.1515/reveh-2015-0040
Received October 12, 2015; accepted March 10, 2016; previously published online April 22, 2016

Abstract: Fibromyalgia syndrome (FMS) is a clinical disorder predominant in females with unknown etiology and medically unexplained symptoms (MUS), similar to other afflictions, including irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), post-traumatic stress disorder (PTSD), Gulf War illness (GFI), and others. External environmental stimuli drive behavior and impact physiologic homeostasis (internal environment) via autonomic functioning. These environments directly impact the individual affective state (mind), which feeds back to regulate physiology (body). FMS has emerged as a complex disorder with pathologies identified among neurotransmitter and enzyme levels, immune/cytokine functionality, cortical volumes, cutaneous innervation, as well as an increased frequency among people with a history of traumatic and/or emotionally negative events, and specific personality trait profiles. Yet, quantitative physical evidence of pathology or disease etiology among FMS has been limited (as with other afflictions with MUS). Previously, our group published findings of increased peptidergic sensory innervation associated with the arteriovenous shunts (AVS) in the glabrous hand skin of FMS patients, which provides a plausible mechanism for the wide-spread FMS symptomology. This review focuses on FMS as a model affliction with MUS to discuss the implications of the recently discovered peripheral innervation alterations, explore the role of peripheral innervation to central sensitization syndromes (CSS), and examine possible estrogen-related mechanisms through which external and internal environmental factors may contribute to FMS etiology and possibly other afflictions with MUS.

***Corresponding author: Phillip J. Albrecht,** PhD, Integrated Tissue Dynamics, LLC, 7 University Pl, Rensselaer, NY 12144, USA, Phone: +518-505-7429, Fax: +518-262-5799, E-mail: philalbrecht@intidyn.com
Frank L. Rice: Integrated Tissue Dynamics, LLC, Rensselaer, NY, USA

Keywords: blood supply; estrogens; homeostasis; pain; skin.

Introduction

A wide variety of intractable enigmatic afflictions share medically unexplained symptoms (MUS) that include varying chronic severities of diffuse pain, fatigue, sleep disturbance, depression, and cognitive impairment often referred to as "brain fog". External environmental factors, including toxins or viral and bacterial pathogen infection, leading to immune and/or neuroendocrine system dysfunction have been overtly implicated in the etiology of several common afflictions with MUS, including irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), multiple chemical sensitivity, electromagnetic sensitivity, sick building syndrome, and Gulf War illness (GWI) (1–3). Stressful external stimuli, and particularly a heightened psychogenic responsiveness (i.e. catastrophizing), are also frequently associated with disorders having MUS, including post-traumatic stress disorder (PTSD) and fibromyalgia syndrome (FMS) (4–6). Polymorphisms involving specific lipids, enzymes, and neurotransmitters have also been implicated as potential mediators of afflictions with MUS, including FMS (7–10). Importantly, steroid hormones also play critical roles in the physiologic responses to external environmental stressors (e.g. trauma), and in maintaining internal environmental and mental homeostasis, as evidenced by a higher incidence of disorders with MUS, as well as depression and anxiety among females in the general population (11–14). There is now substantial evidence implicating estrogens as key mediators of the stress response, including immune, vascular, and nervous system effects (15–18), however, the pathogenesis and/or mechanisms of disorders with MUS and links with environmental stressors are poorly understood. Consequently, these disorders are compounded by a lack of consensus on diagnostic criteria in the absence of identifiable pathologies, and the ineffective and inconsistent response to common therapeutic strategies. These

challenges continue to contribute to suspicions about the validity of the MUS, particularly the notion that these types of disorders constitute purely psychologic issues (i.e. malingerers). However, such suspicions are largely belied by the abrupt onset and severity of many afflictions with MUS, even among previously successful highly motivated and high-functioning individuals.

The external and internal environments both exert essential influences on health and well-being. The mechanisms by which environmental stimuli impact physiology are known to include alterations of neuro, immune, and endocrine functions. External environmental pressures lead to biologic responses that are immediate, often transient, and measurable at the molecular, cellular, and behavioral levels (e.g. c-Fos transcription, NGF release, paw withdraw). The external environment influences physiologic responses across a continuum, where traumatic physical injury represents one extreme, with gradations of influence (e.g. pinprick) continuing to include more subtle, perceived stimuli, which arise from non-physical external environmental contexts (i.e. altered temperature). Furthermore, psychosocial stressors can create negative internal mental environments and altered physiologic functioning. Prolonged or exaggerated internal mental stressors (psychogenic) have associated physiologic disease, particularly among the cardiovascular, endocrine, gastric, and cutaneous systems, and often interferes with cognition.

Importantly, positive individual environmental health practices, for example, routine exercise and/or mindfulness, have been shown to have a strong correlation with improved medical outcomes. Indeed, mind/body connections have been noted in medicine as early as Hippocrates (ca. 460–377 B.C.) and are now fully appreciated among Western medicine based from the demonstrations of physiologic responses being conditioned by external stimuli (Pavlov), psychoanalytical recognition of unconscious emotional conflict (Freud), coupled with work on physiologic changes following emotional stressors (Cannon), which altogether set the biologic framework underpinning psychosomatic disorders, but also represents the theoretical mechanisms of biofeedback, meditation, and other mindfulness techniques. Thus, the environment as discussed here must include *all influence elements:* the 1) external physical and emotional stressors (e.g. trauma) (19), 2) physical and emotional soothers (i.e. massage, food/music), 3) psychosocial percepts (negative and positive), and 4) the internal environment mediated through autonomic homeostatic regulation and consciousness (i.e. subvocalizations). Altogether, these environments directly set the affect (mind) of the individual and drive physiologic response (body) at the molecular, cellular, behavioral, and likely systems levels. When a condition with MUS arises, as exemplified by FMS, impacts from the disorder affect all these environments, and each of these environments directly contribute to the disease process (shown in Figure 1).

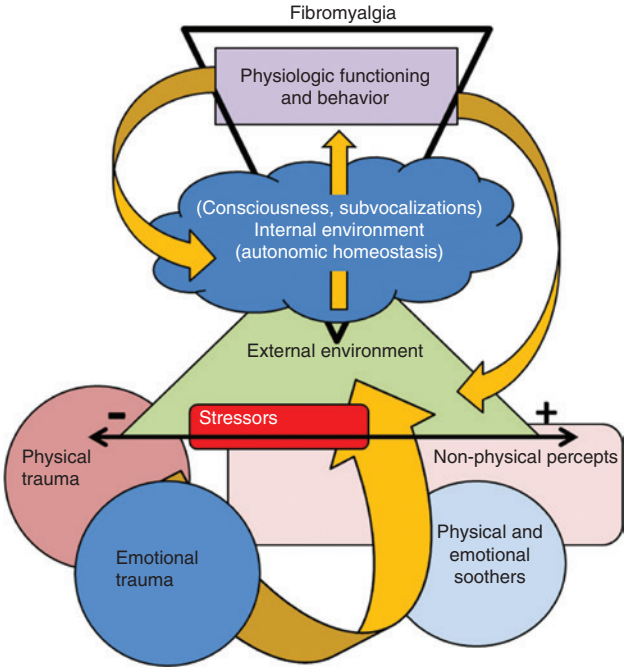

Figure 1: A simplified Venn-map of environmental stimuli and FMS. The Venn-diagram map shows the flow of environmental stimuli while approximating interactions. External environment stimuli exist along a dual continuum from physical to non-physical stimuli and across negative to positive influences. Physical trauma often encompasses elements of emotional trauma and both represent extremes of negative influences. Stressors impart negative influence and can involve non-physical percepts. Physical and emotional soothers represent more positive influences and can include non-physical percepts, which also have a degree of negative to positive influence. All contribute to the total external environment influence. The external environment directly regulates the internal environment, which is created from subconscious autonomic homeostatic mechanisms and conscious subvocalizations. The internal environment, which *encompasses* an individual's affective disposition, will directly influence both physiologic functioning and behavior, both of which influence the internal and external environments, respectively. Increased negative influence from external stressors and/or decreased external soothers can create a negative internal environment through dysregulated autonomic homeostasis and/or negative subvocalization (i.e. catastrophizing; type D personality). In FMS, altered central processing of stimuli and debilitating changes in physiologic functionality may be related to events that skew these environments toward negative influences. A feed-forward cycle can become established whereby a negative internal (affect) environment continues to drive altered physiology and behavior, reinforcing the negative influence of the external and internal environments.

Although documenting the validity of afflictions with MUS provides a current challenge for the biomedical community, the prevailing theory supports a concept of central nervous system (CNS) dysfunction of unknown origin, which renders the CNS overly responsive to stimuli that would be within the normal range of sensory perceptions among healthy individuals. This process is referred to as central sensitization and several disorders with MUS have been classified as central sensitization syndromes (CSS), including FMS (7, 20, 21). However, the mechanisms that underlie the development and maintenance of CSS are still in question. This review focuses on FMS as a model affliction with MUS, examines peripheral innervation alterations associated with this CSS, and explores mechanisms for the role of environmental factors, both external and internal, that may contribute to FMS etiology and possibly other afflictions with MUS. Particularly, attention is focused on recent peripheral cutaneous innervation pathologies (epidermal and vascular) discovered in FMS, which may have an estrogen-dependent mechanism, and likely represents a direct driver of hyperactivity within the CNS, as well as be causative of generalized fatigue, muscle pain, and cognitive dysfunctions (22–24). Currently, the existence of similar PNS vascular innervation pathologies and the role of estrogens in other afflictions with MUS, have yet to be investigated.

Fibromyalgia syndrome

FMS is now a widely recognized and researched medical condition characterized by MUS, which effects anywhere from 2% to 5% of the US population in a female-dominated proportion (20, 23, 25, 26). Still, this multi-faceted disorder remains without a clearly defined etiology, clinical consensus of disease, or effective treatments (26–29). FMS is a polysymptomatic disorder generally characterized by chronic wide-spread deep musculoskeletal pain, coupled with additional debilitating symptoms, including fatigue, non-restorative sleep, cognitive dysfunction, sensory sensitivities (visual, auditory), and autonomic and/or hormonal dysregulation, among others (23, 24, 26–29). The identification of wide-spread musculoskeletal pain has a longer than 120-year medical history, and in 1990 the first standardized FMS-defined criteria were established to set apart FMS from other painful disorders, such as rheumatoid arthritis (RA) (30). These clinical diagnostic criteria were based upon patient-subjective ratings of specific tenderpoints, which were recently noted to be very similar to the 1890s-defined Charcot's hysterical zones (31), and which were updated in 2010 to include additional features of FMS, including sleep disturbances and cognitive declines through the use of the symptom severity score (SSS) and the widespread pain index (WPI) (28, 32), and which even more recently have been updated to include the polysymptomatic distress (PSD) categories to further delineate FMS (29, 33). However, these advances in FMS diagnosis remain subjective diary and questionnaire measures, and do not offer a quantifiable measure of FMS. Similarly, research on quantifiable endpoints [e.g. enzyme-linked immunosorbent assay (ELISA) measures of cytokine blood levels, genetic markers, tissue morphology] have each shown significant differences among small cohort studies, but none has a definitive link across a large random sampling (23, 24, 34, 35). Thus, the FMS community remains with no quantifiable blood or tissue diagnostic test for FMS, and no unified conclusion as to disease etiology, leaving the question of: "What causes FMS and potentially other MUS?" unanswered.

Environmental factors

For this article, the consideration of environmental impacts on FMS and MUS processes attempts to include external and internal factors (as depicted in Figure 1). Therefore, an essential point to consider is specifically what, if any, environmental health events may likely have predisposing, causative, or triggering role(s) in the development of FMS. Physical trauma and psychosocial emotional trauma offer relatively clear segregations of environmental stressors, while the daily social context (e.g. lifestyle habits, stressors) and intrapersonal environment of the individual also represent essential internal factors, all of which are at the center of the FMS and MUS debate (2, 5, 6, 10, 21). Furthermore, critical factors of gender and age participate in environmental influence, both of which are immutable and directly impact the FMS/MUS population. For example, females are prone to diagnosis of FMS ~3× that of males with an age of onset often 45–55 years (21, 29, 36), and increases in age tend to increase the FMS severity (37). Although gonad hormones are obviated in these gender differences, environmental impacts on estrogen and the downstream consequences of physical or psychosocial trauma are not fully known. Furthermore, the impact that environmental stressors, including overt trauma, impart varies distinctly with age, such that early life events may predispose an individual to a heightened response to a similar event even after a prolonged delay (i.e. early-life vs. mid-life) (38).

The external environment exists on a continuum whereby events that are traumatic hold near-permanent

salience and relevance, potentially dictated by physical deformation/damage, along a perceived linear line to the most subtly perceived and even unperceived autonomic-driving sensory input. Similarly, joyous or soothing events hold salience, and these events can produce the same conditioning impact as traumatic events (39–41). Importantly, the feed-forward processes that reinforce a negative internal environment (as depicted in Figure 1), demonstrate that fear/avoidance/denial conditioning as a result of trauma and/or affective pain (real or perceived) can skew homeostatic regulation and lead to pathology (i.e. PTSD). Similarly, it should be noted that a feed-forward process that reinforces internal excitement/anticipation/reward as a result of pleasurable experiences may result in a type of pathology [i.e. post-pleasure addiction disorder (PPAD)]. Clearly, external and internal environmental conditions produce pain/fear or pleasure responses which provide ample psychologic motivation to drive behavior and memory salience, and estrogen has been strongly linked to the mechanisms underlying alterations in hippocampal tissue morphology and physiology (42).

Physical trauma

There is still considerable debate as to the direct connection between physical injury per se and the subsequent development of FMS. For example, whiplash injury has been studied to assess the rates of FMS development with conflicting results. In these reports, some data appear to support a causal effect while others suggest no connection exists. In the counter argument, researchers showed that once adjusted for psychosocial traits (i.e. pre-crash behavior), the physical injury did not predict the development of FMS. However, it has been noted that physical and/or sexual abuse positively correlates with the occurrence of FMS (21, 38, 43). Additionally, physical and sexual abuse has been associated with it a high degree of emotional trauma and stressors related to myriad concerns, including fears of recovery, social acceptance, and changes in quality of life. Thus, the separation of physical trauma from emotional distress adds a strong confound to interpretation (44). To be sure, the question of physical trauma directly leading to FMS, or any affliction with MUS, remains a controversial topic at the center of litigation suits.

Psychosocial trauma

The debate over psychologic trauma being causative in FMS has also been longstanding. Indeed, a condition with very similar symptomology of FMS, occurring in the female population more than males, and with associated MUS, has been identified for over a century (31). However, the disorder remained without a definitive cause or pathology, and was ascribed as a psychosomatic disorder. A still widely held belief is that FMS does not represent organic disease, but is in fact a dimensional or continuum disorder (28, 45, 46). The evidence to support psychologic trauma in FMS is similarly cofounded by physical trauma, as the two often reside together (47). Persons with only psychologic trauma, for example, the loss of a parent at an early age or neglect without physical abuse, have been shown to have altered levels of autonomic functioning and increased stress-related hormone production as adults, symptoms also seen in FMS, and believed to be causative (21). Similarly, poor familial relations and low socioeconomic status predict the development of FMS and wide-spread pain in later life (38, 48), likely as a result of the influence of lifestyle, as discussed below.

Stressors

Severe physical and psychological events, either short-term or long-term and occurring at any time across the lifespan, are considered traumatic. However, highly relevant negative events that do not represent overt trauma are best described as stressors. Stressors from the external environment can impact an individual across all sensory inputs and have a strong negative influence on the internal environment, driving negative subvocalizations (i.e. catastrophizing) and alterations in autonomic homeostasis. Unlike distinct trauma events, stressors may be constant or variable in intensity, but often tend to have a long-term duration that continually drives the relative saliency. Particularly, the biomedical effects of chronic low-level “negative environmental” influences (stressors) include a host of disorders with MUS including pain, anxiety, fatigue, and depression across a wide array of clinical syndromes. That perceived psychosocial stressors can manifest as acute disease has been well-established, mediated through autonomic nervous system (ANS) functioning and the effects of long-term stress on hormone production (i.e. estrogen), which directly effects the nervous, immune, vascular, and endocrine systems.

Interpersonal and lifestyle traits

The human response to common environmental stressors has been utilized to characterize certain personality

traits which can be associated with patterns of rearing and experience. For example, individuals identified as type A (characterized as competitive, hostile, impatient with time-urgency), develop a range of physical (i.e. cardiac) disorders at a far greater risk than those with type B (characterized as non-competitive, non-confrontational, relaxed) personality traits. The type D personality – the *distressed* – is characterized by negative affectivity and severe social inhibition, which describes patients who experience increased negative emotions and tend to inhibit the expression of these emotions in social interactions (49–52). The role of type D personality has been well-established as a causative factor in cardiac disorders (53), and in a 2013 abstract presentation for the European League Against Rheumatism (EULAR) it was reported that the type D personality was associated with 56% of FMS patients, compared with 13%–24% of the general population and 43% of chronic-pain patients (54). These studies, along with numerous others, indicate that personality traits are intimately linked with physical diseases, and these factors are likely contributing to afflictions with MUS, including FMS.

Neurological considerations

Central sensitization

The etiology of FMS, as with other afflictions with MUS, remains debated as being organic or a dimensional disorder graded along a continuum. For example, in a brief response to a 2014 clinical review of FMS, the respondent authors questioned the very usefulness of FMS diagnosis, citing that FMS fits more into a category of PSD, which is classified as a somatic symptom disorder in the DSM-5 (28, 46). Currently, the prevailing hypothesis of FMS postulates that pain pathways in the central nervous system have become globally sensitized (CSS), accompanied by evidence of altered neurotransmitter levels and inflammatory cytokines in the CSF (20, 25, 55–59). Under normal functioning, primary peripheral sensory axons activate the CNS spinal cord and brainstem neurons that create specific sensory pathways that are integrated (i.e. synapse) in the thalamus and in cerebral cortex to drive activation and conscious sensory perception. The CNS sensory system includes specific pathways dedicated to noxious sensory inputs and the processing of these signals to produce "painful" perceptions, but also to drive the activation of descending brainstem control systems that can inhibit or enhance noxious sensory inputs from the periphery (60–62). Among FMS and other painful chronic conditions (i.e. low back pain) a loss of cortical volume among regions associated with pain processing have been detected (37, 63–65). Because overt pathology has been difficult to confirm and the chief complaint of pain experienced in FMS and other MUS is most often wide-spread, a dominant theory of general CSS has emerged. However, the source and/or maintenance of the CSS have not been determined. ANS dysfunction represents another well-documented possible mechanism of FMS, and recent research has provided evidence of peripheral pathologies in FMS, including small fiber loss from the epidermis, altered sodium channel expression in DRG, and altered innervation to arterio-venous shunts (AVS) in glabrous hand skin (23, 35, 66, 67), which may all play critical roles in CSS. Proposed mechanisms for central sensitization include increased spontaneous activity of spinal and brainstem level neurons due to loss of PNS innervation (e.g. deafferentation), hyper-responsive entrainment of CNS neurons by hyper-active nociceptors (e.g. long-term potentiation, kindling), loss of brainstem inhibitory regulation at the spinal level, enhanced intersegmental and/or suprasegmental sensory integration, and alterations in thalamocortical sensory processing loops, effects potentially mediated by excitatory neurotransmitters and/or inflammatory cytokine production (68–70).

Clinically, the diagnosis of FMS no longer requires the use of specific peripheral tenderpoints, however, hypersensitivity to pressure applied in approximately 11 out of 18 specific locations still represents a common finding, including among the hands of FMS patients although not a characterized FMS tenderpoint site. Importantly, the hands have been used for pain threshold testing, blood flow measures, and biopsy assessments in FMS (23, 71–73). Particularly, a striking neuropathology associated with the innervation to glabrous AVS, structures that have critical roles in total blood compartment apportioning, implies altered functionality. Resultant blood flow mismanagement may directly contribute to the excessive fatigue and wide-spread deep pain associated with FMS, symptoms which are thought to be caused by peripheral tissue ischemia and hyperactivation of deep tissue nociceptors as a result of anaerobic metabolites and inflammatory cytokines, a process that would drive and maintain CNS sensitization (23, 74, 75). Furthermore, a source of additional ischemia may also arise from hyperactivity of sympathetically mediated vasoconstriction, a process which can be greatly exacerbated by external and internal environmental stressors (76–78).

Peripheral neural mechanisms

Somatosensory innervation to the skin, muscle, and organs originate from primary sensory neurons of the dorsal root ganglia (DRG) responsible for bridging the peripheral (PNS) and central (CNS) nervous systems. Electrophysiology and psychophysics studies have now established that noxious peripheral stimuli are transmitted through a subset of primary cutaneous and visceral sensory neuron axons that are classified as "C-fibers", which lack myelin and have relatively slow rates of axon conductance, and "Aδ-fibers", which are lightly myelinated and have relatively moderate conduction rates. Collectively, these specific peripheral neurons are termed "nociceptors" (Latin 'nocere' – to injure) (79, 80). With very few exceptions, C and Aδ fibers terminate in peripheral tissues as free nerve endings (FNE) with an unbranched or simple branched ending morphology. Several types of nociceptors have been distinguished electrophysiologically and pharmacologically as being preferentially activated by one or more varieties of noxious thermal, chemical, and/or mechanical stimuli which are perceived as painful in humans or that elicit pain-related behaviors in non-human animals. The ability of specific populations of nociceptors to preferentially respond only to particular types of thermal, chemical, or mechanical stimuli or to combinations thereof (i.e. polymodal) have been attributed to the expression of unique and particular combinations of molecular receptors and ion channels (e.g. transient receptor potential channels – TrpV1, TrpM8, TrpA1), which have individually been implicated pharmacologically and physiologically in responding to specific types or combinations of noxious stimuli (81–86). Peripheral primary sensory nociceptors provide the source of inputs into CNS pain pathways, leading to cortical activations implicated in conscious, discriminative pain perception and the subconscious affective malaise indicative of stress and or discomfort/pain (87).

Peripheral mechanisms attributed to chronic painful conditions include increased spontaneous or ectopic activity and/or hypersensitivity among the wide varieties of nociceptors. For example, the extensive small caliber innervation terminating in the epidermis of the skin has received particular attention as a potential source of chronic pain perceived as originating from the skin. As demonstrated by Hou et al. (88) under a variety of severe regional chronic pain conditions of indisputable peripheral neuropathic origin, such as post-herpetic neuralgia (PHN) and painful diabetic neuropathy (DN) in humans or experimental nerve manipulations in non-human animals, a surprising paradox arises where the epidermal innervation density is commonly and persistently reduced compared to non-diseased humans or control animals (Figure 2). This seeming contradiction may be explained by electrophysiological assessments of impacted peripheral sensory nerves which have revealed increased spontaneous activity, hyper-responsivity to noxious stimuli (hyperalgesia), and de novo responsivity to non-noxious stimuli such that these now elicit painful sensations and behavioral responses (allodynia). Thus, in these conditions with a known small-fiber loss, the initiating peripheral inputs into the CNS pain pathways are in themselves sensitized, a process referred to as "irritable nociceptors", presumably as a result of pathologies in their molecular, neurochemical, and/or morphological characteristics (80).

Importantly, included among the C and Aδ nociceptor inputs into pain pathways are axon types that are preferentially responsive to non-noxious thermal and

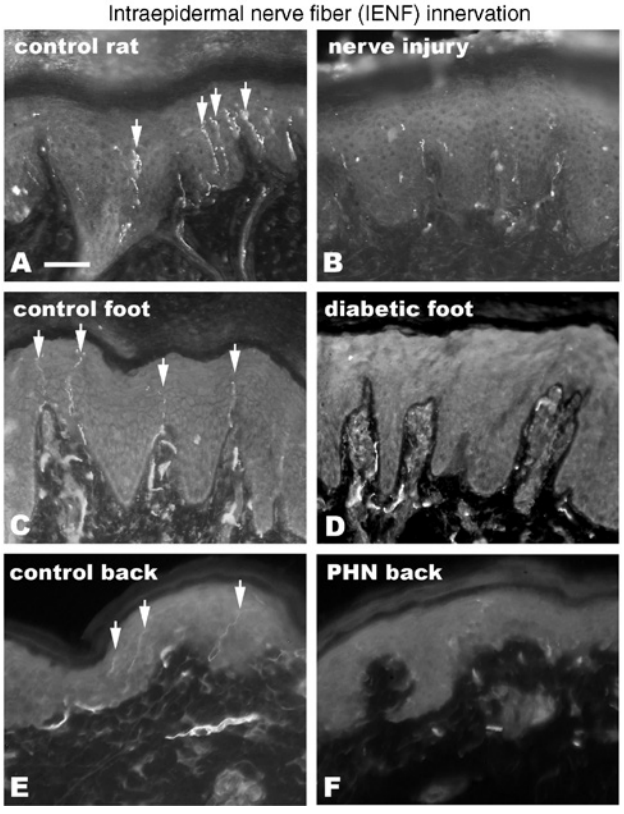

Figure 2: Intraepidermal nerve fiber (IENF) innervation loss is detected among numerous disorders characterized by chronic pain, including overt nerve trauma, metabolic disorders, and viral infections.
IENF are depicted by white arrows in A, C, E to demonstrate the loss of IENF following spinal nerve ligation injury in rats (compare A and B), human painful diabetic neuropathy (DN, compare C and D), and human post-herpetic neuralgia (PHN, compare E and F). See Ref. (88) for additional study details. Scale bar=50 μm for A–F.

mechanical stimuli involved in normal tactile sensation. Often overlooked in chronic pain research is the potential contribution of the large caliber "Aβ-fibers" and specific populations of small caliber C- and Aδ-fibers whose different varieties of terminals are activated by extremely light mechanical stimuli (low threshold mechanoreceptors, C-LTM). Aβ-fiber connections in the CNS generally follow separate pathways from those affiliated with C- and Aδ-fibers, but have points of convergence with nociceptive signal processing in the spinal cord, brainstem, thalamus, and cerebral cortex. Indeed, mechanical activation of these Aβ-fibers can modulate pain perception under normal conditions and may directly contribute to chronic pain under pathological conditions (62, 80).

These peripheral observations raise the question of whether central sensitization represents: 1) an ongoing response to continued hyperactive sensory input; 2) a permanent consequence of transient hyperactive peripheral input; or 3) altered functionality derived independently of the peripheral sensory input. These concepts are based on differing causative roles for CNS sensitization. The first implies that peripheral alterations continue to evoke heightened CNS responses, the second implies that heightened CNS responses remain and/or progress long after transient peripheral hyperactivity returns to normal, and the third implies that an intrinsically originating central phenomenon renders the CNS pain pathways hyper-responsive to normal sensory inputs. Currently, none of these options have been ruled out and none are mutually exclusive of the others, with each possibly being at play in afflictions with MUS.

Recently, several studies have now shown that small-fiber epidermal innervation is significantly reduced across several skin sites among cohorts of FMS patients, whose source of pain is idiopathic (i.e. not attributed to a known disease mechanism) (23, 35, 67). Moreover, electrophysiological assessments of the sural nerve in FMS patients have revealed increased spontaneous activity and hyperresponsivity to noxious and non-noxious stimuli applied to the dorsal foot. Although these observations are similar to those made on regional chronic pain afflictions where the pain is perceived as cutaneous in origin (e.g. CRPS), FMS pain is more widespread and associated with deep tissue origin, which presumes that the loss of epidermal innervation is predictive, and the PNS hyperactivity is widespread and most likely also involves deep tissue afferents (23, 89).

Lost among the emphasis on C-and Aδ-fibers as nociceptors involved in pain mechanisms, is evidence that many if not most C- and Aδ-fibers are likely metabotropic sensors involved in monitoring and regulating normal tissue homeostasis at a subconscious level. Many of these fibers terminate among the same CNS pathways implicated in conscious discriminative pain perceptions as well as subconscious affective stress. Indeed, it seems illogical that the so-called silent nociceptors are normally dormant only to become active under enhanced immune or endocrine challenge and chronic pain conditions (80). A more plausible role would be continuous monitoring of complex multi-molecular aspects of tissue homeostasis; conditions which are not replicated by experimental test stimuli used to elicit electrophysiologically detectable activity. In fact, one could argue that even the electrophysiologically defined nociceptors, which are only activated by noxious test stimuli, do not maintain the high-fidelity synaptic connections required for noxious transmission while being continuously inactive. Under normal conditions, it is a rather rare occurrence that a single ending would encounter a noxious stimulus. However, those pathways retain a high degree of salience and signal fidelity, implying a constancy to the activation. Consequently, we hypothesize that it is among these convergent neural pathways for pain and homeostasis that mechanisms for afflictions with MUS, like FMS, CFS, IBD, and others are likely to be found, and thus, warrant further investigation.

Autonomic nervous system, cytokines, and peripheral cutaneous vasculature

Much evidence has now linked sympathetic ANS dysfunction (hyper- or hypo-), and altered immune system cytokine functioning with many chronic pain conditions, including FMS and other afflictions with MUS (3, 90–94). As well, a consistent loss of small caliber peripheral intraepidermal nerve fibers (IENF; see Figure 2) has now been linked to chronic pain conditions caused by trauma, metabolic dysfunction, and viral infection [e.g. CRPS type-1 (CRPS-1), painful diabetic neuropathy (PDN), PHN, human immunodeficiency virus-1 (HIV-1)], and to disorders without distinct nerve trauma, including FMS (23, 35, 67). The current prevailing evidence of chronic pain mechanisms postulates a link between genetic predispositions, environmental influences, altered ANS functionality, immune system cytokine production, and peripheral neuropathy, although the precise role of IENF pathology in chronic neuropathic pain remains unclear (95–99).

Furthermore, here we make note of the study by us (23), which revealed a significant peripheral neuropathology among the dermal innervation to AVS in the glabrous palmar skin of female FMS patients (Figure 3) (23). AVS are discreet vascular sites predominately found in glabrous

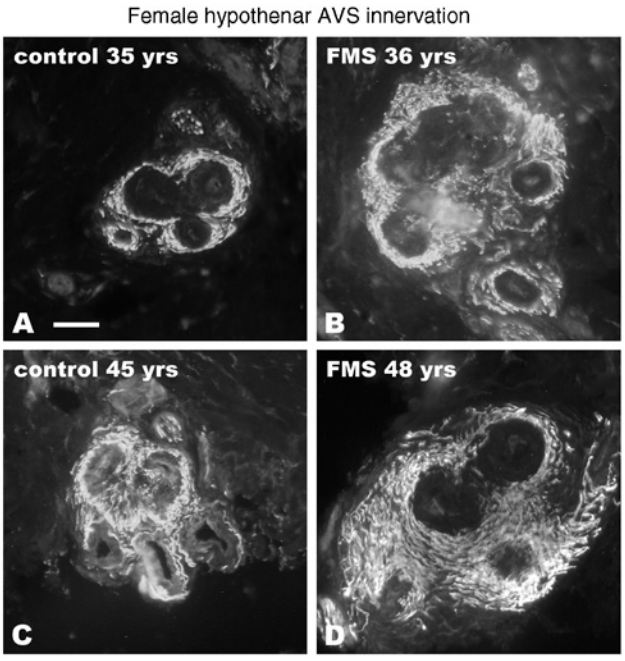

Figure 3: Arteriovenus shunt (AVS) innervation appears exuberant among FMS patients.
Control hypothenar biopsies from different aged subjects (A and C) have less total innervation to AVS structures than age-matched FMS biopsies (B and D). See Ref. (23) for additional study details. Scale bar=25 μm for A–D.

skin which are characterized by dense small-fiber sensory and sympathetic nervous system innervation under ANS control, which modulate vascular dynamics, cellular diapadesis, and the of potential for cytokine production (100). A dense noradrenergic sympathetic innervation to cutaneous arterioles and AVS has long been implicated in vasoconstriction to apportion blood flow for metabolic and thermal regulation. However, an equally dense convergence of sensory innervation to arterioles and AVS, consisting of several types of molecularly distinct C- and Aδ-fibers, has received little attention (22, 23, 62, 101). Although the different types of vascular sensory innervation suggests that they monitor different features of vascular perfusion such as the rate and pressure of blood flow, as well as blood-borne metabolites, little is known about their specific functional properties (62, 80). The varieties and density of the cutaneous vascular sensory innervation is especially pronounced in the glabrous skin of the hand, which in humans is not only especially important for tactile perception and exploration, but also for thermoregulation due to an exceptionally high vascular density and a high surface to volume ratio which play an important role in heat retention and dissipation to maintain a constant core body temperature. As such, distal glabrous skin surfaces have unique, exceptionally well-innervated AVS which serve to regulate blood flow into or out of the dense superficial capillary network. It is estimated that as much as 60% of the microvascular blood volume in humans is located in the skin and 70% of this is in the hands and feet, despite the fact that they have a low metabolic demand (102–104). Additionally, subtypes of these vascular fibers express ligand and thermal gated ion channels (i.e. TrpV1), channels responsive to mechanical stimuli and lactic acid (i.e. ASIC3), and GPCR histamine receptors (62, 80, 81, 105). Of particular interest, is that most varieties of the vascular sensory fibers contain the neuropeptide transmitters Substance P (SP) and CGRP, which are directly implicated in inflammatory pain when released from central terminals in the spinal and brainstem segmental levels of nociceptive pathways and neurogenic inflammation when released from the peripheral terminals around vasculature. SP and CGRP are potent vasodilators with evidence that they are released by the peripheral sensory terminals around blood vessels in an effector vasodilatory function that may be the antagonist counterpart to the vasoconstrictive sympathetic innervation (80, 106–110). Importantly, the sensory innervation also expresses the α2C GPCR, and noradrenergic stimulation has previously been shown to inhibit presynaptic release of SP and CGRP (111). Thus, the sympathetic innervation may mediate vasoconstriction by acting directly on the vascular smooth muscle, as well as inhibiting sensory mediated vasodilation. Therefore, the identified increase in AVS vasodilatory peptidergic innervation and subsequent functionality would result in altered global blood flow dynamics and apportioning, leading to ischemia events, and providing a mechanistic basis for the spectrum of FMS symptoms and possibly other MUS (23, 24, 112). Furthermore, there is evidence demonstrating that peripheral sensory innervation is estrogen-dependent; however whether this underlies a morphologic alteration of AVS and microvasculature following trauma and/or prolonged stress remains unclear (113, 114).

An important case study provides some insight into the potential functional complexities of the sensory innervation to cutaneous microvasculature. Recently, our group analyzed multiple skin biopsies from a very unusual patient (JW) in his late 30s whose primary complaint was extremely excessive sweating (hyperhidrosis). The patient was under evaluation by neurologist Dr. David Bowsher who was a pioneer in research on rare patients born with congenital insensitivity to pain. Lacking the ability to perceive pain, these unfortunate individuals typically have severely mangled extremities, as well as severe mental

handicaps and especially dry skin (anhidrosus). These symptoms are attributed to a congenital lack of small caliber C- and Aδ-fibers, as well as the autonomic fibers that subserve sudomotor functions, which are also small caliber. Although the primary complaint of JW was hyperhidrosis, his medical history revealed a lifetime of serious injuries which he failed to perceive as painful. However, JW was not self-mutilating and had normal intelligence. A rigorous clinical assessment of his tactile capabilities revealed a severely reduced capacity (at least two standard deviations below normal) to perceive all modalities of skin sensation, including light contact, vibration, thermal detection, as well as noxious stimuli. Yet, surprisingly, JW had a nearly normal capability of tactile task performance including the ability to perceive object textures, shapes and thermal properties. Most importantly, immunochemical assessments of the multi-molecular and structural properties of the cutaneous innervation revealed an absence of small fiber innervation to the epidermis, as well as an absence of the many types of Aβ-fiber terminals that are assumed to provide the basis for normal tactile perception. However, JW had a nearly normal sensory and autonomic innervation to his cutaneous arterioles, precapillary arterioles and capillaries, suggesting that these different varieties of vascular fibers were providing his capability for conscious tactile perception (22).

The convergence of the vasoconstictive noradrenergic sympathetic innervation with vasodilatory sensory innervation having receptors for NA, leads us to question whether the beneficial effects of serotinergic/noradrenergic re-uptake inhibitors (SNRI) in treating certain chronic pain conditions and afflictions with MUS, including FMS, could potentially have efficacy at the convergent peripheral innervation on cutaneous blood vessels, and not just centrally (115–117). For example, although the significant neurovascular pathology was a limited observation in only one skin site, there are several implications consistent with FMS symptoms and the documented benefits of SNRI. First, the excessive sensory innervation is consistent with what many FMS patients describe not as overt pain, but aching and tenderness in their hands during high use repetitive tasks. Second, the AVS play an important role in thermoregulation and a common FMS symptom is discomfort during thermal challenges, especially cold temperatures during which dilation of the AVS (likely mediated by the vascular sensory innervation) would divert blood flow from the superficial capillaries directly to venules to conserve heat. SNRI may provide some benefit by prolonging the availability of sympathetically released NA, which may act to modulate the excess sensory innervation-mediated vasodilation.

Importantly, the hyperinnervation of the AVS in the palms could potentially contribute to widespread deep pain of FMS patients by interfering with proper redistribution of blood flow to skeletal muscle under increased demand. The rationale for this speculation is based on several known aspects of vasoregulation that lacked a cogent rationale. As was noted earlier, the microvasculature of the skin, especially the hands and feet can contain a surprising high proportion of the total blood volume, beyond that needed for their low metabolic demands. One implication of this is that the excess blood flow provides a means of dissipating heat to maintain a core temperature especially by constricting AVS to routing blood flow to superficial capillaries. When it is necessary to conserve heat during cold environmental challenges, the total blood flow into and out of the hand and, therefore, to the capillaries is reduced by sympathetically mediated vasoconstriction of the arterioles and AVS. An unexplained observation is that at especially cold temperatures a sudden increase in total blood flow occurs into and out of the hands, but without an increase in blood flow to superficial capillaries. One potential mechanism for this unexplained phenomenon would be a sensory mediated dilatation of the AVS which would open a low resistance bypass to the venules which would further reduce flow to the capillaries. In view of the excess sensory innervation to the AVS in FMS patients, this could account for the discomfort experienced especially at colder temperatures. Moreover, another inexplicable vasoregulatory observation is a drop in temperature during the onset of exercise which increases skeletal muscle metabolic demands. In this case, the excessive blood flow to the hands has been hypothesized to provide a strategic reserve that can be diverted to musculature in response to physical demands. During continued exercise resulting in an internal thermal increase, blood flow returns to the hands to dissipate heat as the muscles transition to anaerobic metabolism with a concomitant increase in lactic acid. Taken altogether, these findings imply that a neurovascular pathology involving the cutaneous AVS could have far-reaching systemic homeostatic effects which would contribute to widespread FMS other MUS of deep tissue pain, fatigue, and possibly sleep disruptions.

Discussion

Major challenges confront the treatment of people suffering from enigmatic debilitating afflictions characterized by MUS such as widespread, diffuse chronic pain, chronic fatigue, and cognitive dysfunction. Most importantly is a

lack of consensus among the medical professionals about the categorization and diagnosis of different types of afflictions with MUS, especially with limited consistently detectable, measurable, and verifiable molecular, structural, and/or physiological pathologies to support the MUS. In general, on a patient-by-patient and physician-by-physician basis, doubts persist about whether these afflictions stem from diseases with underlying treatable and/or preventable pathophysiology and/or elements of psychopathology, or whether they are purely psychosomatic (i.e. how does one distinguish between those who are truly sick and those who are malingerers). Clearly, there is a connection between external environmental experiences (e.g. trauma, socioeconomic lifestyle, or consistent, low-level stress-related factors), the resultant internal environment and personality psychology, coupled with individual genetics, which are all involved in the etiology and persistence of afflictions with MUS, including FMS.

Nonetheless, among patients who describe MUS of chronic widespread pain, fatigue, and cognitive abnormalities, large cohorts of patients exist worldwide who share additional physical symptoms such as IBS and/or skin rashes (eczma, psoriasis), which may be associated with the response to common or shared physical or stressful environmental experiences, including during formative years. Many of the patients have family members who also have hypersensitivity symptomology, adding to the possibility of a genetics component, but also to the idea of environmental negative affective contributions (i.e. learned sick behaviors), while still others represent formerly healthy, highly motivated individuals who have gradually or abruptly become severely debilitated, with categories of afflictions with MUS emerging that reflect these symptoms and suspected etiologies such as multiple chemical sensitivity, extreme electrochemical sensitivity, sick building syndrome, GWI, and PTSD. Given that now enough evidence has accumulated to legitimize several of these obscure afflictions with MUS, a major challenge is to determine why these patient cohorts emerge from a majority of other subjects confronted with the same/similar external environmental conditions. Particularly, are there genetic and/or experience-related environmental factors (trauma, psychosocial) that predispose an individual to developing MUS?

Regardless of the suspected etiologies, yet another major challenge of afflictions with MUS including pain, fatigue, sleep disorders, skin rash, bowel or cognitive dysfunction is that the existing therapeutics provide inconsistent marginal relief with undesirable and often debilitating side-effects. A clinical goal is matching the appropriate treatment to the appropriate patient, and therefore an overarching question is whether there is a shared pathophysiology underlying these shared MUS symptoms. This review focused on FMS, for which there have been several recent neural-related discoveries that may be of relevance to afflictions with MUS, which have not been extensively investigated, particularly related to estrogen-responsive cutaneous vascular innervation. Currently, sensitization of the CNS resulting in an increased systemic hyper-responsivity to sensory input represents a common theory, however this does not explain all the symptoms of FMS or other MUS, including fatigue, sleep disturbances, and cognitive dysfunctions. Consistent with the belief that FMS is a CNS disorder, therapeutics that provide some relief for FMS (e.g. SNRI) are believed to act exclusively within the CNS. Now, several studies have shown that FMS patients have a peripheral IENF pathology similar to neuropathic conditions originating from defined afflictions such a PHN and PDN. As well, a neurovascular AVS pathology identified in FMS may be associated with SNRI efficacy. The etiology of this pathology remains to be determined, but conceivably external and internal environmental factors could impact and promote the proliferation of the sensory innervation, possibly under the control of the female hormone estrogen as a driving factor (23, 113, 114, 118), which may exacerbate this type of vascular pathology and predispose certain individuals to developing FMS or other afflictions with MUS. Currently, the degree to which external environmental stressors and resultant internal environmental status relate to this type of peripheral pathology remain largely unknown, and warrant further investigation. In theory, as further research proceeds regarding these types of possible mechanisms for idiopathic diseases, fewer MUS will exist.

Competing interests: The statements made in this review are solely of the authors, and are not associated with any past or current clients of Integrated Tissue Dynamics, LLC., nor is any of this work to be construed as medical advice. The authors declare no financial conflicts of interest in publishing this work.

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