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REVIEW ARTICLE

An Evolutionary Stress-Response Hypothesis for Chronic Widespread Pain (Fibromyalgia Syndrome)

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Abstract

Objective. The study aimed to seek a unifying biological basis for the phenomena encompassed in fibromyalgia syndrome (chronic widespread pain and associated morbidities).

Setting. While much progress has been made in the last decade in understanding chronic widespread pain, its pathogenesis remains stubbornly obscure and its treatment difficult. Two themes are gaining currency in the field: that chronic widespread pain is the result of central sensitization of nociception, and that chronic pain is somehow related to activation of a global stress response.

Design. In this article we merge these two ideas within the perspective of evolutionary biology to generate a hypothesis about the critical molecular pathway involved in chronic stress response activation, namely substance P and its preferred receptor, neurokinin-1 (NK-1R), which has many empirically testable implications.

Conclusion. Drawing on diverse findings in neurobiology, immunology, physiology, and comparative biology, we suggest that the form of central sensitization that leads to the profound phenomenological features of chronic widespread pain is part of a whole-organism stress response, which is evolutionarily conserved, following a general pattern found in the simplest living systems.

Key Words. Stress Response; Central Sensitization; Substance P; Neurokinin-1 Receptor; Fibromyalgia; Evolutionary Biology

Introduction

Chronic widespread pain affects 2–7% of the population of most countries [1], and carries substantial socioeconomic costs for societies as well as for patients and their families [2]. Fibromyalgia (FM), the diagnostic label given to people with diffuse, persistent pain and mechanical allodynia disproportionate to demonstrable tissue damage, nevertheless remains a problematic construct, not least due to the absence of a cogent model of pathogenesis [3]. Common comorbidities, which constitute the FM "syndrome," include sleep disturbance, fatigue, irritable bowel symptoms, and alterations in mood and cognition [4]. The features of this phenomenology accord with "stress" or "sickness" responses that are found widely throughout the animal kingdom [5,6].

FM has been increasingly attributed to central sensitization of nociception [7,8], an experimentally defined phenomenon of neural plasticity. Central sensitization is characterized clinically by hypersensitivity to mechanical stimuli, and neurophysiologically by significant increases in the membrane excitability and synaptic efficiency of spinal neurons involved in nociception, coupled with reductions in counteracting inhibitory pathways [9–11]. Central sensitization can plausibly account for key pain-related features of FM [8] and for some, of its comorbidities (such as sleep disturbance, irritable bowel, headache) [8] but not for all of them (such as affective disorders or cognitive impairment).

In this article, we merge the thesis that the phenotype labeled clinically as FM involves central sensitization of nociception with the intuition that this reflects activation of a whole-organism stress response [12–15]. Furthermore, we suggest that this activation of a global stress response in humans follows a general pattern found in the simplest

living systems. From this perspective, chronic widespread pain becomes one manifestation of prolonged or undampened activation of a complex, evolutionarily conserved system designed to defend against and repair the organism following perceived threats to homeostasis.

Underpinning the recent promulgation of central sensitization as a key to understanding FM and its comorbidities is the recognition that the neuropeptide substance P (SP), which has long been the most robust biochemical indicator of FM [16], has been shown to be necessary for the development of central sensitization [17]. We suggest that elevated levels of SP and its preferred receptor, neurokinin 1 (NK1R), not only indicate an unresolved stress response, but also are critical to the pathogenesis of FM.

Stress Responses

Organisms from bacteria to humans actively maintain themselves far from thermodynamic equilibrium by seeking out resources necessary to manufacture the components that preserve system integrity [18,19]. Because their milieu is never static, organisms continually alter their structure (that is, their components) and adapt their interactions with features of their milieu. The result is homeostasis, the state of dynamic systemic balance maintained by an organism's physiological organization and behavioral repertoire [20].

Given this basis, all states of affairs salient to the organism are perceived in one of three ways: as acceptable or adequate for continued homeostasis (OK); as challenging or threatening to homeostasis (OK^{-}); or as facilitating enhanced functioning (OK^{+}) [21]. The set point for such assessment is determined by the current state of the individual organism, as interpreted by its total biological organization. Factors contributing to this interpretation include immediate homeostatic parameters and the state of the environment, but also genetic, developmental, and cognitive factors. In the case of group-living organisms, social factors condition responses as well. This is as true of bacteria as it is of humans [22].

Any state of affairs that challenges its homeostasis presents a *stress* stimulus, or stressor, to the organism [23]. Stressors may be external (environmental) or internal (physiological, psychological) [24]. All organisms have a repertoire of physiological and behavioral processes to meet perturbations that are perceived as threatening to survival [25]. Patterns of response that facilitate an organism's adaptation to homeostatic challenge are called *stress responses*. A stress response thus can be viewed as the organism's pattern of reaction that something, either within itself or in its surrounding milieu, is OK^{-}. The stimulus may be life-threatening or merely perturbing; it may be the lack or the presence of something, but it is sensed as challenging the organism's current set point for adequate functioning in such a way that defensive action is necessary.

While the concept of a stress response clearly exists in mammalian neuroimmunology, neuroendocrinology, and behavioral science, its functional characterization is somewhat vague beyond the general notion of a coordinated response to perturbation that "improves the ability of the organism to adjust homeostasis and increases chances for survival" [24]. The common denominators of bacterial stress responses are more perspicuous [25,26], and evidence suggests these broad features are also common to mammalian (including human) stress responses. These common denominators include:

- A dynamic, evolving trade-off between growth/reproduction and maintenance/repair [5], usually involving changes in expression of hundreds of genes [10].
- Elevation of reactive oxygen species (ROS) and the negative impact of allostatic load [27].
- Protective (hormetic) effects against subsequent stress from short-term stress response activation [28,29], but degeneration of multiple vital systems when activation is prolonged [30].
- The critical role of communication molecules in inducing and/or coordinating stress responses [31,32].
- And high phenotypic variability among individuals in a population [33].

SP and Stress

One of the earliest neurosignaling molecules discovered [34], SP is an 11-amino acid peptide of the tachykinin family that is biologically active at extremely low concentrations [35]. While not without exception, the general signature of SP release and/or activation of NK1R is stimulation, excitation, and arousal [36–38]. The primary activity of the SP/NK1R pathway, which is virtually ubiquitous throughout the body, appears to be associated with responses to homeostatic challenge; indeed, SP was once hypothesized to be an important marker of the body's "network of defense" [39]. Intriguingly, the SP/NK1R pathway shares features with almost all of the common denominators of stress responses found in prokaryotes.

In mammals, SP and NK1R are most strongly associated in the central nervous system (CNS) with the hypothalamic-pituitary-adrenal (HPA) axis [40], the body's primary "stress" circuit and the brain's main interface with the immune system [41], with the affect-generating limbic system [42], and with the dorsal horn of the spinal cord, the central nociceptive pathway [43]. The HPA-immune axis is the system typically presumed to be disordered in stress response hypotheses of chronic widespread pain [14].

Classically associated with nociception, the sensing of noxious stimuli that in humans can be experienced as pain, SP has long been referred to as a "pain transmitter" [44]. Nociception induces the organism to protect itself (usually a damaged area), reduce general activity (often manifest as fatigue or depression-like symptoms), and to avoid the noxious stimulus in future [45]. Nociception thus

is strongly linked to cognition (external-sensing modalities, memory, information processing, learning) and affect (valuation of incoming stimuli, arousal, vigilance, mood). Cognition and affect constitute a vital network of subsystems for sensing and dealing with danger, particularly unpredictable or novel threats [46], and the SP/NK1R pathway is strongly implicated here, too, in positive and aversive reinforcement learning [47], territorial aggression [48], affective disorders [49,50], and, more recently, addictive behavior [51].

Long held to be a peptide of exclusively neuronal origin, SP is produced by a variety of inflammatory cells, including eosinophils, macrophages, lymphocytes, dendritic cells, and mastocytes [35,52]. So potent a stimulator of proinflammatory cytokines is the SP/NK1R pathway that one investigator wondered whether all inflammatory processes have "a requisite requirement for SP" [53]. Other defense- and repair-related activities associated with the SP/NK1R pathway include: up-regulation of "stress" hormones, such as norepinephrine and the precursors of cortisol, corticotropin-releasing hormone and adrenal corticotrophic hormone [54]; down-regulation of endogenous opioids such as met[hionine]-enkephalin (MENK) [55,56] and other putative "feel-good" neurotransmitters, such as serotonin [57]; stimulation of contraction and increased motility in the gut [58,59]; vomiting [60]; vasodilatation [61]; histamine release [62]; production [63] and migration [64] of new cells to damaged tissue; defensive alterations in cardiac [65] and respiratory [65] function; and edema following head injury [66].

In its role in central sensitization, about which more later, SP is involved in what appears to be the activation of a "phenotypic switch" that produces profound and durable (if reversible) neuronal changes involving the altered expression of large numbers of genes [10]. While known mostly as pronociceptive, SP can also be antinociceptive, or protective, at very low doses [67]. As a potent stimulator of cytokines, SP/NK1R stimulate secretion of myriad signaling molecules [32]. The SP/NK1R pathway is also known to be a potent inducer of ROS, and possible oxidative stress, in a wide variety of tissues [68–71]. Thus, although necessary for physiological defense, the activity of SP/NK1R is increasingly recognized to be "double-edged" [72], and is now believed to be critical in the pathogenesis of emphysema [65], brain damage resulting from trauma-induced edema [66], pathological scarring [72], and cardiomyopathy following infection [73]. The SP/NK1R pathway has also been implicated in some autoimmune disorders [74,75].

In view of this substantial body of evidence, we hypothesize that SP/NK1R is an important (possibly the most important) biomarker of states of affairs the organism perceives as threatening (OK^{-}), and plays a critical role in both the maintenance of the stress response and the physiological damage that can be induced by its prolonged activation. In short, SP is one of the body's critical frontline defense molecules against existential stressors. However, being a relatively blunt instrument, its effects can be widespread and damaging if its release is not effectively modulated.

The Role of SP/NK1R in Central Sensitization

Sensitization is a form of conditioning that involves the amplification of a response following repeated administration of a stimulus. Increase in the synaptic strength of neurons following repeated stimuli, called long-term potentiation, is a kind of sensitization believed to underlie memory. The increased effect of a drug in an addict after a period of abstinence is another kind of sensitization. The stimulation of peripheral nerves when skin is rubbed repeatedly will create a warm sensation that eventually will become painful. When noxious stimulation is sufficient to damage tissue, continuing pain and sensitivity to innocuous stimuli may result.

In the early 1980s, Woolf developed an animal model to determine whether post-injury pain hypersensitivity resulted from reductions in the threshold of peripheral nociceptors or from an increase in the excitability of CNS neurons involved in processing of noxious sensory input [76]. This led to the discovery that noxious peripheral stimuli could induce long-term changes in the excitability of spinal cord neurons. At the core of central sensitization is the phenomenon of neuronal plasticity, the capacity of neurons to adapt to changing conditions by altering their function, structure, and/or chemical profile [11]. Central sensitization is defined as "an enhancement in the function of neurons and circuits in nociceptive pathways [in the dorsal horn of the spinal cord] caused by increases in membrane excitability and synaptic efficiency as well as to reduced inhibition" [10].

Long-term potentiation involves the movement of calcium ions across the neuronal membrane at the synapse [77,78]. In lamina 1 of the dorsal horn, believed to be critical to the sensitization process leading to hyperalgesia [9,79], the SP/NK1R pathway regulates the movement of calcium in glial cells as well as neurons [80], the latter in tandem with the excitatory amino acid glutamate, with which SP is co-released [81,82]. In glial cells, SP promotes calcium release by mobilizing stores from within the cell, whereas in neurons, SP induces calcium to enter from the extracellular milieu [80].

The potential importance of the SP/NK1R pathway to central sensitization was first suggested with chemical ablation of spinal neurons expressing NK1R in lamina I [79]. This resulted behaviorally in significant reduction in responses to noxious stimuli (e.g., capsaicin, inflammation, nerve injury) and resulting hyperalgesia. Not only were the responses of NK1R-expressing neurons to different noxious stimuli dramatically reduced, but also nociceptive windup, which normally follows capsaicin treatment, was also virtually absent, suggesting that NK1R-expressing neurons are a "pivotal component of the spinal circuits involved in triggering central sensitization and hyperalgesia" [17].

The role of SP/NK1R in stimulating calcium influx helps to explain the efficacy of pregabalin, originally developed as an antiepilepsy drug and the first pharmaceutical approved by the US Food and Drug Administration for FM treatment [83]. By binding to a protein associated with voltage-gated calcium channels, pregabalin "modulates neuronal calcium influx" apparently by reducing "release of several pain pathway neurotransmitters, such as glutamate and SP" [83].

Evidence for Evolutionary Conservation of SP

Given the importance to survival of reacting appropriately to noxious stimuli, Woolf and Salter propose that the development in organisms of "the capacity to detect and remember danger" via neuronal plasticity and central sensitization may have been the result of "a major evolutionary drive" (p. 1,765) [11]. SP belongs to an evolutionarily conserved family of brain/gut peptides that act in the nervous systems, muscles, and viscera of a wide variety of organisms, invertebrates, and vertebrates [84,85]. Studies in mammals and phylogenetically distant vertebrates identify a conserved role for SP in neuroimmune function and physiological repair [86].

One line of evidence suggesting the evolutionary vintage of SP in the human stress response comes from human ontogeny. Immunohistological studies on tissue from aborted fetuses found that SP appears simultaneously with acetylcholine (ACh) and MENK, early in human development—at 5–7 weeks in spinal cord and 10 weeks in brainstem nuclei [87,88]. By contrast, serotonin, neuropeptide Y, vasopressin, oxytocin, and other neurotransmitters do not appear in human fetal development until weeks 10–12 [89]. The "overlapping localizations" of SP, ACh, and MENK in many regions of the CNS led the researchers to speculate that interactions among these macromolecules might be "important for the proper establishment of the neuronal circuitry" [89]. Nicotine studies using slices of rat brain demonstrate that SP, ACh, and MENK strongly regulate one another in vitro [90,91].

In in vivo animal studies, the ACh-SP-MENK triad is involved in regulating the neuroimmune response and timing of mammalian circadian systems. A cholinergic antiinflammatory system functions to prevent defensive (SP-induced?) physiological responses from endangering the organism via overshoot [92]. By contrast, the endogenous opioid MENK exerts "a dual immunomodulatory effect": higher doses suppress while lower doses enhance neuroimmune response [93]. In the regulation of N-methyl-D-aspartate-induced release of ACh during the 24-hour cycle, NK1R has been shown to be involved in the morning release of ACh, which together drive arousal, whereas in the afternoon, NK1R interacts with μ-opioid receptors (MOR), to which enkephalin binds, to control cholinergic transmission [94], suggesting an inhibiting influence in preparation for rest.

The early appearance of SP in the company of ACh and MENK supports the thesis that the adaptive responses of many (possibly all) organisms occur along a dynamic continuum (OK, OK^-, OK^+), based on the tolerability of current circumstances relative to the organism's current state. The diverse role of SP in responding to OK^- states of affairs has been discussed. Acetylcholine, a ubiquitous neurotransmitter active in the CNS and peripheral nervous system, is highly associated in mammals with normal waking behavior [95] and plays an important modulatory role in a many physiological systems, and so is a plausible candidate for a "normalizing" (OK) factor. MENK has long been associated with reward [96,97] (OK^+) and antinociception [98].

The stress response hypothesis advanced here helps to makes sense of another recent twist in the FM story. A long-standing puzzle of FM treatment is the clinical finding that morphine and other exogenous opioids are not as effective in treating FM-related pain as they are other forms of nociception. Recent brain imaging studies have shown that the binding potential of MOR is significantly reduced in FM patients in brain regions associated with nociceptive processing [99]. As mentioned above, MENK is the primary endogenous ligand of MOR, and animal studies show that SP and MENK closely interact, generally negatively. MENK can modulate the nociceptive effects of SP, but SP/NK1R can also override the MENK/MOR pathway. Interestingly, NK1R have been found to regulate morphine-induced endocytosis and desensitization of MOR in central neurons, at least in animals [100]. The hypothesis predicts that, relative to FM, a persistently activated SP/NK1R-driven stress response would effectively override MENK/MOR-induced modulation of that response. Together, these two studies suggest a possible mechanism: the reduced binding potential of MOR seen in FM patients is due to elevated SP/NK1R, which reduces the number of MOR available for MENK or opiate binding via endocytosis or desensitizes those available, or both. If the studies are replicated, these findings would be consistent with a critical role for SP/NK1R in the pathogenesis of FM.

SP and Clinical Presentations

As evidence for its association with pain grew in the 1980s [101–103], SP became a logical target for investigation in chronic widespread pain, the diagnostic label for which shifted from fibrositis to FM [104]. So dramatic were the differences in cerebrospinal fluid concentrations of SP (SP/CSF) in the earliest studies of FM patients (mean 36 fmol/mL) compared with healthy controls (mean 12 fmol/mL), that researchers suggested SP/CSF could be a biomarker for the syndrome [105]. These results were consistently replicated in other studies of FM patients [57,106–108], although studies using other assays, notably serum, returned inconsistent results [109].

Because of the strong link with nociception, antagonists to SP and NK1R were pursued as analgesic therapies for FM and other forms of pain [110]. What should have been a "straightforward, landmark triumph of science" [111] proved elusive, however, as the drugs did not perform as

hoped [110]. This may explain why research into SP/NK1R and chronic widespread pain fell off dramatically in the past decade. However, significantly elevated SP levels have been found in other chronic pain conditions [112], such as daily headaches [113], migraine [114,115], and whiplash-related neck or shoulder pain [116].

Largely unnoticed has been the finding of elevated SP in comorbidities often reported with FM, including irritable bowel syndrome [117,118], sleep disturbance [119,120], and mood changes [121], including major depressive disorder (MDD) [122,123]. As in FM [124,125], stress has been implicated in each of these conditions. Admittedly, due to small numbers of patients in many of these studies, the findings must be regarded as preliminary. However, elevated SP levels are not found in all FM comorbidities, such as chronic fatigue syndrome, which suggests that real differences exist between the two syndromes [126].

Perhaps most striking of all is the well-established clinical and biochemical overlap between patients with chronic widespread pain and patients suffering from posttraumatic stress disorder (PTSD), a syndrome defined as a pathological response to stress. Not only do about half of patients with PTSD meet the diagnostic criteria for FM [127], but also PTSD sufferers have also been shown to have substantially elevated SP/CSF levels [123]. A large telephone survey of community-based women in New York and New Jersey several months before and after the terrorist attacks on the World Trade Center on September 11, 2001, reaffirmed the close linkage between FM and PTSD [128]. Individuals reporting symptoms of FM before the attacks were much more likely to report symptoms of PTSD after the attacks, which suggested to the researchers a common factor in the pathogenesis of these two syndromes.

The connection between FM and explicit stressors that could be perceived as life-threatening is equivocal but suggestive. A recent meta-analysis of sexual abuse and lifetime diagnosis of somatic disorders found no statistically significant association between sexual abuse and FM relative to controls until analysis was restricted to studies in which sexual abuse was defined as rape, when significant associations were observed with lifetime diagnosis of FM [129]. Similarly, a study of the role of violence in the development of FM did not find a statistically significant association until the frequency of abuse was considered, which was "positively and significantly correlated with FM [130]." Finally, in a recent study of survivors 3 years after a major train crash in Israel, 15% met the American College of Rheumatology (ACR) criteria for FM [131].

Just as individual variability is a signature of stress responses in general, significant variability is apparent in SP/CSF findings in FM patients. Early studies reported SP/CSF levels ranging from only slightly above the normal baseline to six times the normal baseline [105]. This sort of variability, also found in other studies, does not appear to correlate with symptom duration, age or gender, and may point to genetic and/or developmental factors. Evidence for a genetic predisposition to chronic widespread pain is growing [132]. Although not conclusively established in relation to chronic widespread pain, response to stress is known to be susceptible to adverse early developmental influence [133–136]. The high variability in SP levels may also point to multiple stressors; however, the highest SP/CSF levels were found in smokers [105].

Given continuing controversy over the "psychosomatic" nature of chronic widespread pain, it is interesting that SP release can be induced by "psychological" as well as "physical" stimuli. In a US study of a small number of combat veterans with PTSD or MDD who were willing to endure in-dwelling spinal catheters over many hours, levels of SP/CSF sharply increased above an already elevated baseline when these patients were shown a combat-related video, but did not change when they were shown a video with neutral content [123]. Mice subjected solely to chronic restraint, a murine model of psychological stress, developed SP-mediated responses in the gut that can be damaging when prolonged [137]. This is not to suggest that chronic psychological stress will lead in a significant proportion of cases to development of FM. Rather, it is simply to show that psychological stress has been shown to correlate with elevated SP, and that one possible outcome of prolonged psychological stress—for example, that associated with early sexual abuse—is development of FM.

Discussion

On the basis of evidence from diverse disciplines, we have argued that chronic widespread pain is one manifestation of persistent activation of an evolutionarily conserved physiological system designed to defend and repair the organism from challenges perceived to threaten homeostasis. At the core of this system is the SP/NK1R pathway.

The merit of an hypothesis generally rests on its ability to do at least three things: to bring a greater degree of explanatory coherence to diverse existing data; to provide explanations for seemingly anomalous or new findings; and to make testable predictions [138]. The SP/NK1R stress response hypothesis presented here meets these criteria in at least five ways.

First, the SP/NK1R stress response hypothesis explains why a chronically activated, unresolved stress response might manifest as labile widespread pain, and why such pain is rarely a single-symptom presentation. With reference to the comorbidities of FM and its overlap with PTSD, the hypothesis posits that they also are manifestations of a hyperactive or chronically (re-)stimulated stress response. Differences between individuals in clinical presentation reflect that stress responses are subject to a high degree of genotypic and phenotypic variability across the living world. From an evolutionary perspective, variability is a virtue.

The SP/NK1R stress response hypothesis arguably provides support for the recent introduction by the American

College of Rheumatology of new diagnostic criteria for FM, which abandons the tender-point count established in 1990 as the diagnostic hallmark in favor of a continuum view of so-called "fibromyalgianess" [139,140]. However, if SP measurement is to be useful in the clinical setting, a robust, less-invasive, and more economical diagnostic alternative to the gold standard of CSF sampling must be developed. If such a method of measuring SP becomes generally available, our hypothesis predicts that SP will indeed serve as a reliable biomarker for chronic activation of the stress response.

Second, our hypothesis also suggests why FM patients develop diverse symptoms associated with other stress-related disorders (i.e., irritable bowel, sleep disturbance, depression), but that patients for whom these stress-related disorders are the primary clinical presentation do not generally develop FM. The hypothesis predicts that central sensitization of nociception is a critical factor in the pathogenesis of FM. Once this postulated phenotypic switch has been "thrown," as it were, other disorders associated with SP/NK1R elevation are more probable, depending on individual phenotypic vulnerabilities. By contrast, in the absence of central sensitization, or a primary nociception-related presentation, patients suffering from other stress-related disorders are less likely to develop FM.

Third, the SP/NK1R stress response hypothesis may help to explain three unusual findings. We have already noted earlier how the hypothesis relates to the recent finding of reduced MOR binding potential in several pain-processing brain regions in FM patients. Brain imaging studies of patients suffering from different conditions characterized by pain (such as FM, phantom pain, chronic back pain, irritable bowel syndrome, two types of frequent headache) have also identified reduced gray matter volume, which suggests at least that neuroplastic changes may be a factor in the process by which episodic pain becomes chronic [141,142]. More recently, researchers found "a characteristic gray matter decrease" in osteoarthritis patients compared with controls, but discovered that the deficits were reversed after pain-relieving hip surgery, which suggests the gray matter deficits were the consequence, not the cause, of chronic pain [143]. Recent research suggests that SP plays a critical role as an initiator of neuroinflammation following traumatic brain injury and that high levels of the neuropeptide are associated with non-apoptotic neuronal cell death [144,145].

In another discovery, a subset of FM patients was found to have significant cellular changes in skin [146]. SP is released in the skin and has long been associated with flare and itch [147] and, more recently, psoriasis [148], all stress-related conditions that result in cellular changes. In addition, chronic widespread pain is also associated with dermatographia, in which the skin responds with exaggerated wheal and flare to non-noxious mechanical stimulation [149].

Fourth, as we have shown above, the SP/NK1R stress response hypothesis explains how pregabalin works in patients who respond to that drug, by counteracting SP- and/or glutamate-induced stimulation of calcium influx in neurons (and possibly other CNS cells) involved in nociception. It also points to an explanation of why the proportion of drug responders is not higher among FM patients: the stress response apparatus is highly variable from individual to individual for a wide variety of reasons. As Mease and Choy observe, a patient's experience of FM involves "a complex interplay among genetics, developmental influences, triggering factors, and the neurophysiologic and psycho-emotional substrate of the individual" [83, p. 361].

By extension, the SP/NK1R stress response hypothesis also explains why certain "holistic" nonpharmacologic therapies for chronic widespread pain, such as patient education, cognitive-behavioral therapy, and mindfulness/relaxation meditation, appear to help a substantial proportion of patients [150], particularly when combined with exercise [151]. The importance of cognition in triggering and maintaining a stress response is becoming increasingly clear [152], and SP release is susceptible to psychological triggers. On the other hand, the actual performance of exercise indicates to the organism that it is functioning reasonably well. In short, it may take a system approach to treat a system disturbance. If this line of reasoning is correct, we think it unlikely that a pharmaceutical "silver bullet" for FM will ever be found. By contrast, multimodal therapies that address the whole patient should in general complement pharmaco-therapeutic interventions.

Finally, given the dose-dependence of SP/NK1R activity reported in different studies with diverse research goals (higher SP levels correlate with greater symptom severity), it may be that SP/NK1R-mediated responses are cumulative for every stressor in relation to which such responses are stimulated. If that is the case, then SP levels should be higher in those patients with multiple physiological insults, including, say, the concurrence of asthma and chronic bronchitis, two respiratory conditions each individually associated with elevated SP [153].

Conclusion

As have others, we claim that FM is not a distinct clinical entity [154,155]. Rather, we suggest that chronic widespread pain, mechanical allodynia, and their frequently associated comorbidities are manifestations of the prolonged or unresolved activation of an evolutionarily conserved system designed to defend against and repair the organism following homeostatic challenge that can be sensed in a wide variety of ways, including cognitively. By combining the intuition that the central sensitization of nociception that underlies chronic widespread pain is a manifestation of stress response activation with the identification of a candidate pathway, we share the aim of all those who work in and for this clinically frustrating area: to provide better targets for future research and rationales for therapy, as well as a superior narrative for clinicians and

especially patients to make sense of these distressing and debilitating experiences.

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