

Evolution, Stress and Fibromyalgia

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Despite affecting huge numbers worldwide and being researched extensively over 25 years, fibromyalgia syndrome (FMS) remains a problematic construct, for clinicians and patients alike. Characterised by persistent widespread pain and tenderness disproportionate to demonstrable tissue damage, of which there may be none, the syndrome often includes, sleep disturbance, fatigue, 'irritable bowel,' cognitive and affective changes, and, less frequently, skin disorders. Without a cogent model of pathogenesis for this complex syndrome, effective treatment remains elusive.

An evolutionary approach provides insight. Several clinical features of FMS accord with "sickness behavior," found widely in the animal kingdom, which is the observable manifestation of physiological processes working to restore proper functioning. Sickness behavior is part of the organism's response to some sort of stressor (threat, disturbance), which may be perceived via innate immunity or cognitively. The building blocks of the human stress response (i.e., cytokines, neurotransmitters, hormones) are evolutionarily ancient.

The systems that underlie the human stress response (SR) are multiple, co-modulatory and co-regulatory. Almost from the moment a SR is activated, countervailing processes also activate, to ensure that the dramatic molecular events marshaled to save the animal don't themselves do damage. This is because many molecular actors involved in SRs are 'double-edged,' and can have negative as well as positive effects on organism functioning. The response to stress thus is designed to engage, repair, and stop (resolve).

When an SR is prolonged in any organism, for whatever reason, profound changes occur in functioning and behaviour. Chronic SR activation in humans is associated with some of the most medically important diseases in the developed world, including cardiovascular disease, type 2 diabetes, and metabolic syndrome.

One of the Janus-faced molecules involved in vertebrate SRs and associated with a wide variety of chronic human diseases is substance p (SP), a deeply conserved neuropeptide also found in insects and molluscs. In humans, SP operates in both the central and peripheral nervous systems. With its preferred receptor neurokinin-1 (NK1R), SP is involved in a staggering range of defensive mechanisms, including cytokine release, cell manufacture and migration to sites of injury, mast cell granulation, edema, vomiting, gut contraction, cell death, and aversive reinforcement learning. Its importance to human functioning is reflected in ontogeny: SP is one of the first neurotransmitters to appear in foetal development, before other SR actors, including corticotropin-releasing hormone,

adrenaline, noradrenaline, dopamine, and serotonin.

The relevance of SP for understanding FMS is three-fold. First, elevated SP in cerebral spinal fluid is the most reliable biomarker of FMS. Patients typically have SP levels 2-3 times those of healthy controls. Second, SP is highly correlated with the common co-morbidities of FMS, including depression, sleep disturbance, irritable bowel and psoriatic skin disorders. Third, recent research shows that SP is necessary for the development of central sensitization in the spinal cord's dorsal horn. Central sensitization is widely thought to be the most promising explanation of how chronic pain is induced.

From this perspective, FMS can be seen as a clinical outcome of prolonged activation, or dysregulation of a complex, evolutionarily conserved system designed to defend the organism against threat. There are several explanatory benefits to such a view.

First, this perspective explains why a chronically activated or unresolved SR might manifest as labile widespread pain in association with other co-morbidities. Second, it explains the clinical overlap of FMS with post-traumatic stress disorder, which is also associated with elevated CSF-SP. Third, because SR systems are among the most genetically and phenotypically variable systems in biology, this perspective may help to explain the great differences between individuals in clinical presentation. SR systems in mammals are highly susceptible to modification in early development, producing different stress reactivity profiles, so childhood exposures to stressors, including serious disease or injury, may be relevant to clinical presentation.

The SP/SR hypothesis may help to explain why SP and NK1R antagonists did not fulfill their promise as treatments for FMS. SP/NK1R participates in many defensive systems important to whole-organism functioning, not just chronic pain, and they work in combination with many other molecules. Finally, the hypothesis might also help to explain why certain holistic, non-pharmacologic therapies (e.g., patient education, cognitive-behavioural therapy, mindfulness/relaxation) appear to help a substantial proportion of patients, particularly when combined with exercise. It takes a system to treat a system.

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