Complex Adaptive Systems Allostasis in Fibromyalgia

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KEYWORDS

- Fibromyalgia • Autonomic nervous system
- Complex adaptive systems • Allostasis
- Neuropathic pain • Dorsal root ganglia
- Complexity science • Holism

Prevailing linear-reductionist medical models seem unable to explain complex diseases like fibromyalgia (FM) and similar maladies fully. In contrast, paradigms derived from the new complexity theory seem to provide a more coherent explanation for the pathogenesis of these intangible illnesses. Different lines of investigation have shown that patients who have FM experience degradation of their main complex adaptive system, namely, the autonomic nervous system (ANS). It has been proposed that such autonomic dysfunction may cause the multiple symptoms of FM, including chronic widespread pain.[1]

This article is divided into two parts. The first part intends to be evidence based and reviews basic concepts of the ANS related to pain generation. This first part also reviews all controlled studies listed in PubMed looking at ANS performance in FM. The second part of the article contains a holistic pathogenetic proposal for FM based on the new complexity science paradigms. In this second section, ''allostasis'' and ''allostatic load'' are proposed as pertinent concepts for FM. This holistic model intends to be hypothesis generating; therefore, it needs to be tested with appropriate scientific studies.

PART ONE
Autonomic Nervous System: Basic Concepts Related to Pain Generation

The ANS is the portion of the nervous system that controls the function of the different organs and systems of the body. One striking characteristic of this system is the rapidity and intensity of the onset of its action and its dissipation. This unpredictable performance has chaotic features. The ANS is activated by centers located in the

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spinal cord, brain stem hypothalamus, and thalamus. These centers also receive input from the limbic system and other higher brain areas. These connections enable the ANS to serve as the principal part of the stress response system in charge of fight or flight reactions.

The peripheral autonomic system is divided into two branches: sympathetic and parasympathetic. These two branches have harmonious antagonistic actions on most bodily functions; thus, their proper balance preserves homeostasis. The action of these two branches is mediated by neurotransmitters. Catecholamines are the sympathetic neurotransmitters, whereas acetylcholine acts in the parasympathetic periphery.

The naturally occurring sympathetic catecholamines that act as neurotransmitters within the central nervous system are norepinephrine, epinephrine, and dopamine. Norepinephrine also acts in peripheral postganglionic nerve endings and exerts its effects locally in the immediate vicinity of its release, whereas epinephrine is the circulating hormone of the adrenal medulla and influences processes throughout the body. The major metabolic transformation of catecholamines involves methylation and oxidative deamination. Methylation is catalyzed by the enzyme catechol-O-methyltransferase (COMT), whereas oxidative deamination is promoted by monoamine oxidase.[2] The COMT enzyme has been a focus of interest because of its relation to pain susceptibility in healthy women. There are several polymorphisms in the COMT gene that are associated with a defective catecholamine-clearing enzyme. Women who possess these polymorphisms are more susceptible to experiencing pain.[3]

Catecholamines act by binding to adrenergic receptors (ARs). ARs are fundamental parts of the sympathetic nervous system for maintenance of homeostasis. ARs are G-related proteins expressed on virtually every cell type in the body, including lymphocytes and platelets. As result of this receptor ubiquity, sympathetic activation may influence other major networks of the body, such as the immune system or the coagulation system. ARs are subject to many regulatory factors, including desensitization, down-regulation, and internalization. This dynamic plasticity may serve as a buffer against excessive agonist stimulation.[4] ARs are key players in cardiovascular homeostasis, such as blood pressure regulation during orthostatic challenges. ARs are also involved in pain sensitivity. Healthy women with a particular type of β-AR haplotype termed *haplotype 2* are prone to have low blood pressure and to develop chronic painful conditions.[5]

Clinical Assessment of Autonomic Nervous System Function

The complex function of the ANS cannot be properly appreciated with linear methods, such as static blood or urine levels of catecholamines. Changes in breathing pattern, mental stress, or even posture alter the sympathetic/parasympathetic balance immediately and completely. Opportunely, two nonlinear research instruments have been introduced to aid in clinical research of cardiovascular autonomic function: heart rate variability (HRV) analysis and head-up tilt-table test (HUT).[6–8] These two measuring tools have provided important clues to the pathogenesis of FM.

Heart rate variability analysis

This method is based on the well-known fact that the heart rate is not fixed; rather, it varies from beat to beat in a seemingly random way. Computers are able to discern and measure the influence of the sympathetic or parasympathetic branch of the ANS on this constant variability. HRV can be studied in the time domain in which the basic units are milliseconds. Time domain mathematic calculations include, among others, the standard deviation of the duration of all R-R intervals and the percentage of adjacent pairs of R-R intervals that differ by more than 50 milliseconds