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Is it possible to develop an animal model of fibromyalgia?

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Animal models of disease states are valuable tools for development of new treatments, as well as examining underlying mechanisms. An animal model of disease should mimic the symptoms and pathology of the disease and importantly be predictive of effective treatments.

Fibromyalgia is a unique pain syndrome because it is diagnosed by symptoms, not by underlying pathology. In contrast, arthritic diseases are diagnosed by pathology in addition to patient symptoms. The symptoms of fibromyalgia include widespread pain, which includes the trunk, and pain to pressure stimuli at 18 distinct tender points. Fibromyalgia syndrome (FMS) is also associated with a number of other symptoms including fatigue, sleep disturbances, and psychological disturbances, such as depression and anxiety. The prevalence of these symptoms varies across the population, with fatigue occurring in up to 80% of the population, sleep disturbances in 90% and depression occurring in 40% (reviewed in [9]). Thus, an animal model of FMS ideally should include widespread pain and the associated symptoms.

In human subjects some underlying pathological changes have been discovered, yet the initiating cause for FMS is as yet undefined. Neuroendocrine dysfunction, neurotransmitter changes, neurosensory disturbances, as well as genetic predispositions have been implicated in fibromyalgia. The hypothalamic-pituitary-adrenal (HPA) axis is also implicated; there are blunted cortisol responses and abnormal growth hormone regulation ([1]). Decreased serotonin and increased substance P and nerve growth factor are found in the cerebrospinal fluid of patients with fibromyalgia ([1;9]), as is central amplification and reduced central inhibition of pain ([1;9]). Further, there is a strong familial aggregation for FMS, and evidence for polymorphisms of genes in the serotonergic, dopaminergic and catecholaminergic systems (reviewed in [1;9]). Based on the widespread changes in multiple systems, some have suggested that there are multiple causes and that FMS is a manifestation of multiple syndromes with similar symptoms. The development of an animal model is therefore difficult. Thus, multiple potential animal models could be appropriate.

In this issue, Nagakura and colleagues [6] modulated the biogenic amines (serotonin, noradrenaline and dopamine) by delivering reserpine, which depletes biogenic amines throughout the body including both the peripheral and CNS. The animal model results in muscle and cutaneous mechanical hyperalgesia, an expected loss of the biogenic amines in the CNS, and accompanying depression. The hyperalgesia found in this model is reversed by drugs that have clinical efficacy in FMS, antidepressants and anticonvulsants, but not by those without clinical efficacy viz., non-steroidal anti-inflammatory drugs. As such the model mimics the symptoms of FMS with widespread mechanical hyperalgesia and depression, the pathology of FMS with decreases in biogenic amines, and the pharmacological profile for treatment of FMS.

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It remains to be seen if animals treated with reserpine have other symptoms associated with FMS such as fatigue, anxiety, and sleep disturbance.

The following experiments should be considered in order to validate the model. Do the animals treated with reserpine have increased fatigue responses? Do alterations in the biogenic amines result in central sensitization? Does a decrease in biogenic amines also affect the HPA axis? Do alterations in the biogenic amines alter excitatory neurotransmitters, such as substance P or glutamate, or neurotrophic factors? Enhanced fatigue could be predicted as serotonergic neurons mediate fatigue, serotonin enhances motor neuron excitability to alleviate fatigue, and there are alterations in serotonin levels in fatigue conditions ([4]). As there are serotonergic inhibitory pathways to the spinal cord from the brainstem that contribute to analgesia and inhibit dorsal horn neuron activity ([3]), removal of the serotonergic system may facilitate central sensitization. Modulation of the HPA axis by stress also alters the 5-HT system; overactivity of the HPA axis increases release of 5-HT and affects serotonin receptors ([5]). Thus, the model developed by Nagakura et al. may, in fact, mimic the FMS pathophysiology.

It should be pointed out that other models have been developed that similarly mimic the symptoms of FMS. Repeated intramuscular injections of acidic saline results in central sensitization, increased descending facilitation, increased glutamate, and widespread pain (cutaneous, muscle and viscera)([2]). This model, like that reported by Nagakura and colleagues is sensitive to antidepressants and anticonvulsants, but not to NSAIDs [2]. It is also sensitive to exercise [2]. Future studies should determine whether this model is also associated with changes in the biogenic amines, alterations in the HPA axis, and with other symptoms, such as fatigue or depression. Interestingly, a forced swim model of stress-induced hyperalgesia [8] results in widespread hyperalgesia and an enhanced response to inflammatory nociceptive stimuli, subcutaneous formalin and intramuscular carrageenan [8;10]. There is also enhanced activation of central neurons, measured as increased Fos expression, in response to injection of formalin in animals [7]. This stress-induced hyperalgesia model is associated with changes in the serotonergic system and the enhanced hyperalgesic response is reduced by serotonin reuptake inhibitors [8;10]. As stress alters the HPA axis [5], studies of the HPA should also be tested in this model.

The authors of the present paper make a convincing argument that the reserpine model mimics some of the underlying pathology and symptoms associated with FMS. As such, it may be a useful model for understanding the etiology of FMS in the clinic. Whether all features of FMS are manifest in the model, however, remains to be seen. As for inflammatory models, which are thought to mimic various forms of arthritis, each model is unique and may be useful for understanding different aspects of the disease process. The fibromyalgia model adds to an existing body of literature that begins to expand on the consequences of some of the underlying pathology in FMS. The study suggests that global reductions in biogenic amines, as observed in a clinical population with FMS, may be an important contributor to the hyperalgesia and depression observed in people with FMS.

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