

Fibromyalgia and the complex regional pain syndrome: similarities in pathophysiology and treatment

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Abstract

Although the pain of fibromyalgia usually is not preceded by an injury to the involved tissue, whereas that of the complex regional pain syndrome usually starts at a site of prior trauma or surgery, both disorders may share a common mechanism—pathologic sensitization of brain mechanisms that integrate nociceptive signals—and both apparently respond to treatment with ketamine, an anesthetic-analgesic agent whose actions include blockade of *N*-methyl-*D*-aspartate receptors. Ketamine's widespread illegal use as a recreational agent probably precludes developing it as a general treatment of centrally mediated pain disorders; however, its efficacy suggests that related, to-be-discovered agents could be useful.

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This report describes 2 chronic and often debilitating pain syndromes, fibromyalgia and the complex regional pain syndrome (CRPS), which appear to share a common pathophysiologic mechanism—supersensitivity of brain mechanisms that receive and integrate nociceptive signals—and, possibly, a common therapeutic response to ketamine, a drug whose actions include inhibition of the *N*-methyl-*D*-aspartate (NMDA) receptors for brain glutamate. The loci at which fibromyalgia pain is felt are not usually those of prior tissue damage, whereas those of CRPS pain usually (but not always) are sites of a prior injury or surgical procedure. Given ketamine's psychotropic effects, this drug is not an optimal therapeutic agent. However, its efficacy in these pain syndromes suggests that other drugs, awaiting discovery, with similar biochemical actions will find important uses in pain management.

1. Characteristics of fibromyalgia

The name *fibromyalgia* suggests a disorder in which skeletal muscle or its adjacent fibrous tissue is painful or

becomes so in response to use or to physical pressure. Indeed, the most widely used (but challenged as tautological [1]) criteria for diagnosing fibromyalgia—those proposed by the American College of Rheumatology [2]—require only that patients complain of widespread musculoskeletal pain and that they exhibit excessive tenderness when mild pressure (sufficient to cause blanching beneath the physician's fingernail) is applied at 11 or more among 18 predetermined anatomical sites. The musculoskeletal pain and stiffness, though diffuse [3], often start in the shoulders; usually are not preceded by sensory stimulation; are chronic but of variable intensity; and are sometimes associated with sensations of “crawling,” numbness, or burning. Patients also complain that their skin feels swollen. However, no swelling can be observed; nor are there other local signs of inflammation. Most patients also complain of subjective symptoms including nonrestorative sleep, fatigue, anxiety, difficulty concentrating, forgetfulness, and psychological distress. Hence, not infrequently, their initial diagnosis (or ultimate codiagnosis) is major depression. However, as with other chronic pain syndromes, it usually is difficult to determine whether depression is a cause or consequence of the patient's symptoms. The disease reportedly affects 3.4% of women and 0.5% of men in the United States [4]; the basis of this sex difference is unknown.

Because fibromyalgia patients exhibit neither physical signs nor laboratory evidence of any distinct pathologic process, the disease is no longer identified as a “fibrositis”;

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and most investigators interpret its pathogenesis as reflecting disordered central pain processing. Specific central nervous system (CNS) structures that might be involved include the secondary somatosensory cortex, insula, and anterior cingulate cortex, all of which, by functional magnetic resonance imaging, exhibit greater activation in patients given pressure or heat stimuli than in control subjects [5,6]. Three Food and Drug Administration–approved drugs for fibromyalgia now exist; 2 of these (duloxetine and milnacipran) suppress the inactivation (by reuptake) of synaptic norepinephrine and serotonin, whereas the third (pregabalin, which is used in both fibromyalgia and neuropathic pain [7]) combines with a protein ($\alpha 2\text{-}\delta$) associated with voltage-gated neuronal calcium channels, thereby inhibiting calcium influx and the release of neurotransmitters that mediate pain. All 3 drugs are thought to act within the CNS. About half of all patients respond to them, as shown by requiring greater local pressure to produce given levels of pain [8].

2. Fibromyalgia as a dysfunctional pain syndrome

As recently proposed by Costigian et al [9], chronic pain syndromes can be differentiated into 4 main groups: *nociceptive* pain, which occurs normally in response to noxious stimuli and continues only as long as the stimuli are maintained; *inflammatory* pain, which results from tissue injury and the subsequent inflammatory response and disappears after resolution of the injury; *dysfunctional* pain, which is maladaptive, providing neither protection from injury nor support for the healing and repair processes; and *neuropathic* pain, which can follow damage either to peripheral neurons (eg, from mechanical trauma, metabolic disease, neurotoxic chemicals, herpes zoster and other infections, or tumor invasion) or those in the CNS (from cord injury, stroke, or multiple sclerosis). Fibromyalgia's characteristics suggest that, like such diseases as irritable bowel syndrome and interstitial cystitis, it is properly included among the dysfunctional pain group and reflects malfunctioning sensory processing within the CNS. It occurs in the absence of identifiable noxious stimuli, inflammation, or damage to the nervous system; and the pain sensations it generates are compatible with inappropriate amplification of what would otherwise be minor nociceptive signals. Hence, theoretically, an effective treatment of fibromyalgia could be a drug that blocks neurotransmitter receptors that sensitize the CNS neurons that process pain signals, for example, the NMDA receptors [10,11]. As discussed below, available evidence tends to support the view that ketamine, the major action of which is to block NMDA receptors, does indeed reduce the pain of fibromyalgia [12,13].

3. Characteristics of the CRPS

As described in a series of publications by Schwartzman and his associates [14], CRPS is a chronic condition, more

common in women (80%) and first appearing at any age, that is characterized by severe neuropathic pain usually preceded by an injury (77% of cases) or surgical procedure (11%), but sometimes occurring without antecedent tissue damage. The pain is usually described as burning and aching, and exhausting. Among patients in whom the pain does not remit spontaneously, its intensity tends not to decrease with time and may worsen. Most patients (84%–90%) exhibit touch allodynia (ie, enhanced pain when touched or lightly brushed) and static mechanoallodynia (91%–96%) (pain when light pressure is applied); half or more also describe visceral pain.

Patients generally are treated with narcotics, anticonvulsants, nonsteroidal anti-inflammatory drugs, or antidepressants; in general, about one third obtain relief. Unlike patients with fibromyalgia, those with CRPS usually exhibit changes in skin color and temperature at the site of the original tissue injury, suggesting local sympathetic hyperactivity. Most patients also describe loss of strength, difficulty initiating movements, muscle spasm, and abnormal limb posture. More than 80% are forced by their pain to stop working, of whom 70% remain so. More than half also report difficulties with cognition and memory, perhaps a consequence of the chronic pain [15].

4. Treatment of fibromyalgia and CRPS with ketamine

The initial attempt to use ketamine to treat fibromyalgia apparently was that by Sorensen et al [10], based on Cohen and Quintner's [1] suggestion that the tenderness at test sites in patients represents secondary hyperalgesia, and on the evidence from animal studies that NMDA receptors are involved in central sensitization [16]. Among the 11 patients in their study who received the drug (0.3 mg/kg intravenously), 8 exhibited relief of pain; and this effect persisted for 20 to 80 minutes after the end of injection. A subsequent double-blind, placebo-controlled study by Graven-Nielsen et al [17], involving 29 fibromyalgia patients (17 known "ketamine responders") who received intravenous ketamine on 2 occasions, confirmed its ability to attenuate muscle pain and hyperalgesia and suppress temporal pain summation. Subsequent studies, including also those using oral or subcutaneous ketamine, have found significant reductions in pain (by about 50%) among treated patients and positive responses in about half of treated subjects. Attempts have been made, using single photon emission computed tomography imaging [13], to determine whether an individual patient's ability to respond to ketamine correlates with brain blood flow: flow was found to be reduced in the medial frontal gyrus among nonresponders and increased in midbrains of responders. Apparently, no large double-blind, placebo-controlled studies have been performed on fibromyalgic patients given standard doses of ketamine for weeks or months.

Ketamine has been used experimentally to suppress postoperative as well as chronic pain for decades and continues to be prescribed in high doses as an anesthetic or adjunct to anesthesia in children, surgical emergencies, and veterinary medicine. Possibly its earliest applications to patients with CRPS were by Eide et al [18], who described its use, given parenterally, to patients with postherpetic pain; by Takahashi et al [19], who administered the drug epidurally; and by Harbut and Correll [20], who administered it intravenously. Most subsequent studies have also used intravenous infusions of subanesthetic doses, with significant effects on pain and tolerable adverse effects (eg, hallucinations, “feeling inebriated”). Keiffer et al [21] have described a different treatment regimen in which higher, coma-inducing doses (typically 600–900 mg) are administered continuously for 5 days; patients exhibit positive effects that can persist for many months or—with periodic “booster shots”—indefinitely (this treatment is not allowed in the United States but is used in Germany and Mexico). The ketamine has also been administered orally or topically; and in general, most studies have been positive. Although most publications have described single case reports, more recent studies [22] have used randomized, placebo-controlled protocols.

5. Ketamine

Ketamine, a derivative of phencyclidine, is an anesthetic and analgesic, as well as a recreational drug (“special K”) and Schedule III Controlled Substance. It is used, among other things, for induction of general anesthesia in children; to provide sedation or analgesia in emergencies; as a veterinary anesthetic; and, usually with an opiate, to relieve cancer pain. In high doses it can produce psychotropic effects including hallucinations; however, the lower, subanesthetic doses used in most of the above studies usually fail to do so. Its advantages include only minimal suppression of breathing and its failure to lower blood pressure.

Ketamine’s primary mechanism of action is thought to involve noncompetitive inhibition of NMDA receptors, as described above; however it may be notable that another NMDA antagonist, MK-801, fails to induce hypnosis. In high doses, ketamine also can also affect sigma opioid receptors, block muscarinic cholinergic receptors, and potentiate GABAergic neurotransmission. Several publications—including an uncontrolled National Institutes of Health study involving 18 patients with refractory major depression—have described useful antidepressant effects of the drug within hours of its administration [23]. Some long-term users of recreational ketamine describe impairments in memory; however, the drug also has been noted to improve memory in CRPS patients with demonstrated memory impairments.

Ketamine’s complicated history—particularly its widespread use as a recreational drug—militates against recommending it as a treatment of fibromyalgia or CRPS,

except in single-treatment regimens using perhaps-curative coma-inducing doses. However, there seems to be no controversy that it does indeed work in many patients. It can be hoped that analogs will be discovered that lack its psychotropic actions but retain its apparent ability to suppress the brain’s supersensitivity to nociceptive signals that probably underlies these diseases.

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