Pathophysiology of Complex Regional Pain Syndrome

Development of New Treatments

BY ROBERT J. SCHWARTZMAN, MD

COMPLEX REGIONAL PAIN SYNDROME (CRPS), also known as reflex sympathetic dystrophy (RSD), is a chronic pain syndrome that may follow injury to the peripheral nerve or central pain pathway. The nerve injury may involve small C (unmyelinated) or thinly myelinated A-delta fibers (1-4μ) that innervate all tissues. In approximately 10% of patients CRPS is induced by damage to central pain pathways (1,2). The syndrome is characterized by: 1) burning pain, mechanical and thermal allodynia, hyperalgesia, and hyperpathia; 2) autonomic dysregulation; 3) neurogenic edema and hyperhidrosis; and 4) a complicated movement disorder often associated with atrophy and dystrophy. The syndrome frequently follows trivial injury and often spreads over much of the body (3).

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A fundamental concept for understanding this process is the activity-dependent neural plasticity of pain transmission neurons (PTNs) (4). Pain itself may change the synaptic currents of receptors on PTNs and modify their physiologic characteristics. The receptors either fire to stimuli that would not ordinarily cause them to discharge and to maintain this discharge after the stimulus is withdrawn, or they are unable to fire and the patient is hypoesthetic. The basic process appears to be an afferent barrage of mechano-insensitive C-fibers, which activate immediate early response genes (IERGs). These in turn induce the nuclear transcription of new sodium receptors that will be inserted into the firing C and A-delta fibers at the site of injury as well as the synthesis of proteins that are inserted into PTNs and change their firing characteristics.

There is constant communication from peripheral tissue to the dorsal root ganglion (DRG) and the dorsal horn (DH). This is accomplished by means of axonal transport of trophic factors from the periphery (retrograde transport) and antegrade flow of neurotransmitters and newly synthesized sodium receptors (fast axonal transport by the microtubule system) and structural proteins that move through the axoplasm to the area of injury (1,4).

Following injury, four basic systems activate in the spinal cord and throughout multiple areas of the neuraxis: the discriminative and affectual pain system, the sympathetic and motor systems, and the diffuse nociceptive inhibitory control system (DNIC). It is easiest to understand this process by analyzing the events following a fracture. The patient feels and reacts to pain, nocifensor reflexes splint the arm, and the sympathetic system is activated to divert blood from the periphery to the central vascular pool. The DNIC is activated and limits the intensity and spread of pain. CRPS starts as a peripheral condition, but over time becomes centralized.

Review of Postulated Mechanisms Underlying the Pathophysiology of CRPS

AT THE SITE OF INJURY, an "inflammatory soup" of small molecules, prostaglandins, neurotransmitters, cytokines, enzymes, neurotrophic factors, and bradykinin, derived from the blood or inflammatory cells, directly activate the terminal membranes of nociceptive afferents. This process

Robert J. Schwartzman, MD, recipient of the *Richard S. Weiner Pain Education Award*, gave a keynote presentation on the Mechanisms and New Treatment of CRPS.

may cause these afferents to discharge or to become sensitized so that they fire at a lower threshold (5).

The major mechanisms that cause this peripheral nociceptive terminal sensitization are the activation of intracellular kinases (phosphokinase A and C) and phosphorylation of tetrodotoxin (TTX) resistant sensory-specific sodium ion channels (SNS) on nociceptive-afferent terminals. These processes decrease their activation threshold and rate of deactivation, thus maintaining and increasing the injury barrage (6).

Concomitantly, at the site of injury, there is increased production of growth factors from macrophages and lymphocytes, which are retrogradely transported to the DRG and PTNs of the DH that phosphorylate and alter G-protein coupled receptors and ion channels, further enhancing the process by increasing PTN depolarization (1).

Central Sensitization of Pain Transmission Neurons

PERHAPS THE MOST IMPORTANT CHANGE that occurs in CRPS is the sensitization of pain transmission neurons throughout the neuraxis (1,7,8). This process is initiated by high-frequency discharge of mechano-insensitive C-fibers from the injured area. It is characterized by:

1) extraterritorial spread of pain, out of a nerve or root distribution;
2) a lower threshold to depolarize pain transmission neurons of the DH;
3) mechanical and thermal allodynia: an innocuous mechanical or thermal stimulus is perceived as painful;
4) evoked pain which persists when the stimulus is withdrawn: "after discharge;"
5) increased receptive field size: a larger area of the body surface will discharge the DH pain transmission neuron;
6) hyperalgesia: a greater degree of pain than expected is elicited from a slightly painful stimulus;
7) hyperpathia: there is a higher threshold to depolarize the PTN of the DH, but once crossed, the pain reaches maximum intensity too rapidly and persists after the stimulus is withdrawn.

Central sensitization of PTNs is similar to the physiologic process of long-term potentiation (LTP) that has been extensively studied *in vitro* and in the CA-1 region of the hippocampus (8,9,10). LTP causes enhanced synaptic transmission of the involved cell, or its counterpart, long-term depression (LTD), suppresses synaptic currents so that the cell is unable to depolarize. Clinical studies have demonstrated a perceptual correlate of nociceptive LTP and LTD in humans (11).

LTP occurs following a high-frequency, sustained nociceptive barrage—different physiology may depend on frequency and spike timing between pre- and post-synaptic depolarization—that releases glutamate and neuromodulars. One example of this would be the small vasoactive neuropeptide substance P onto a PTN. Glutamate and released neuropeptides cause long-lasting, slow-excitatory, post-synaptic potentials (EPSPs) that last for seconds. These allow for temporal summation, which releases the magnesium block of the N-methyl-D-aspartate (NMDA) receptor that allows calcium and sodium to enter the cell. As will be noted later, the NMDA receptor is the therapeutic target for ketamine (1).

A major component of the plasticity of the synaptic transmission of PTNs occurs at the post-synaptic density (PSD), the post-synaptic membrane that is opposite the C-fiber afferent. It is composed of scaffolding and signaling proteins, which determine function of the PTN after NMDA activation. The number and conductance of post-synaptic a-amino-3-hydroxy-5-methyl-isoxazole-4-proprionic acid (AMPA) receptors is the primary means of enhancing or decreasing synaptic conductance of nociceptive neurons (12,13).

The removal of the Mg++ block from the channel pore of the NMDA receptor initiates the enzymatic intracellular cascades that determine the excitability of the nociceptive neuron, ie, whether it exhibits LTP or LTD. Critical kinases for LTP are calcium-calmodulin-dependent kinase II (CaMKII), ras mitogen-activated protein kinase (MAPK), and inositide 3-kinase pathways. The MAPK pathway seems to be particularly important for the regulation of transcription factors such as cyclic adenosine 5-monophospate (cAMP), response element binding protein (CREB), which is important for gene expression (1,14).

The expression of novel genes is an important mechanism that may change the excitability of PTNs in intractable chronic CRPS patients. In chronic pain, normally somatic fibers start to express markers of pain transmission neurons (SP) and brain-derived neurotrophic

factor (BDNF), and they may act as pain fibers physiologically. In general, the intracellular kinases favor LTP while the phosphatases promote LTD.

LTD features are frequently seen in CRPS, and are usually expressed clinically as hypoesthesia and the inability to appreciate a pinprick or temperature stimulus. It is a complicated process, but appears to depend on a rise in intracellular Ca^{2+} and spike timing between pre- and post-synaptic elements. NMDA-dependent LTD depresses firing of the nociceptive neuron by inducing internalization of AMPA receptors, dephosphorylation of their GluR1 subunits, and increasing AMPA degradation after endocytosis. This process is further boosted by upregulation of γ aminobutyric acid (GABA) and glycinergic-mediated inhibition (15).

Immune Mediated Central Sensitization

NEUROPATHIC AND INFLAMMATORY pain models demonstrate that there is glial activation following nerve or tissue injury. This activation also correlates with allodynia and hyperalgesia. Pretreatment with microglial inhibitors block pain facilitation, but days after pain induction they are ineffective. The signaling molecules important in glial activation are ATP, Cx3CL (fractilakine), CCL1 (monocyte chemotactic protein-1), proinflammatory cytokines IL-1B, IL6, TNF-a, SP, and glutamate (16).

Once activated, microglia and astrocytes secrete proinflammatory cytokines, nitric acid (NO), excitatory amino acids, prostaglandins, and ATP, which influence the induction and maintenance of neuropathic pain. Increased levels of IL-6 and IL-1B have been found in the cerebrospinal fluid (CSF) of CRPS patients as compared with controls (18). Proinflammatory cytokine blocking agents would thus provide another therapeutic target to reduce CRPS pain.

Sympathetic Nervous System and CRPS Pain

IT HAS BEEN KNOWN FOR MANY YEARS that sympathetic activation may exacerbate and maintain CRPS pain (19, 20). Activation is often seen early in the disease process, and in a few patients sympatholysis has cured the illness. Pain relief after a sympathetic blockade outlasts an induced conduction block, and suggests that a sympathetic drive is a mechanism for the maintenance of central sensitization of nociceptive neurons.

Experimental nerve-injury models demonstrate that in the DRG sympathetic fibers sprout and form basket terminals around large mechanoreceptive neurons and thinly myelinated A-delta fibers. This anatomical connection and upregulation of adrenoreceptors that discharge nociceptive afferents are a basis for the coupling of sympathetic and somatosensory systems. In addition to these peripheral connections, noradrenergic neurons influence ascending pain transmission by their interaction with the DNIC, which focuses and limits pain stimuli (21).

New Therapeutic Targets

EXPERIMENTAL NEUROPATHIC PAIN MODELS and clinical experience have shown that blockade of the NMDA receptor on PTNs alleviates neuropathic pain. Malignant intracellular calcium-induced cascades, which transform the excitability of PTNs and the expression of new sodium channels and proteins such as dynorphin, are being unraveled. The bottom line for pain control is that when fewer AMPA fast-pain receptors are incorporated into NMDA receptors, their synaptic efficacy is decreased or they are destroyed intracellularly when the NMDA receptor is blocked. The number of active AMPA receptors and their activity determine the spontaneity and degree of pain.

Ketamine

GLUTAMATE RELEASED from C-fiber nociceptive afferents, in conjunction with glycine, activates the NMDA receptor. Its channel pore characteristics might also be modulated by neurotrophic-factor phosphorylation. Similarly, AMPA receptors can be phosphorylated by phosphokinase A after the magnesium block is lifted from the NMDA receptor by adrenyl cyclase, which changes their activation and deactivation kinetics.

Ketamine blocks the NMDA receptor through agonist activation of its phencyclidine (PCP) receptor site. If given without concomitant use of midazolam and lorazepam, it causes hallucinations and is dysphoric. If ketamine is administered properly with midazolam at the

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beginning and end of infusions, the psychotropic effects can be overcome without difficulty. Ketamine has the strongest affinity for the NMDA receptor that is clinically available. In addition to midazolam and lorazepam, we use small doses of clonidine 0.1 mg with infusions to decrease sympathetic stimulation and to block possible Olney lesions. These are posterior-cingulate gyrus lesions that have been demonstrated in rats exposed to MK801, a stronger NMDA blocking agent.

Ketamine Outpatient Protocol

WE HAVE EMPLOYED AN OUTPATIENT PROTOCOL for early-stage patients that have not responded well to NSAIDs, antiepileptic agents, antidepressants, narcotics, sympathetic blockades, and physical therapy. We always attempt to find a reversible cause of the syndrome, such as a disc, poorly healed fracture, or neuroma, and address the maintaining drive prior to the ketamine protocol.

Our outpatient protocol is administered over four hours. Patients have their blood pressure, EKG, and oxygen saturation monitored. There are always two CPR-qualified infusion nurses in the room and an attending available. Prior to treatment, all patients have had both cardiac and psychiatric clearance. Patients are administered 150 to 200 mg of ketamine over four hours. Two milligrams of midazolam are administered at the beginning and end of the procedure. If patients become nauseous, they are given ondansetron. All patients are given 2 mg of lorazepam to be taken at home for any psychotropic effects. The infusions are given daily for ten days. Boosters of two infusions are given at two weeks, one month, and three months. Eighty percent of patients have had a 60% to 70% reduction of pain that lasts for approximately six months. Several have had almost total relief for eight months (22).

Ketamine Inpatient Protocol

IN MORE SEVERE PATIENTS that have been refractory to all modes of standard therapy, an inpatient protocol is employed. This includes 40 mg of ketamine per hour for five days. The concentrations of ketamine in the bloodstream must reach 250 to 300 μ g/L to be effective. Patients are awake, and if they become dysphoric, are given 2 mg of midazolam supplemented with 1 to 2 mg of lorazepam every four hours.

This protocol has not "cured" anyone, but it does offer approximately 70% relief for three to six months. A few patients have had sustained relief for eight months. The same booster protocol used for our outpatients is employed with inpatients.

Our present focus is to use inpatient and outpatient protocols to block all components of CRPS pain, and then to add inflammatory cytokine blockade to maintain good response. Both thalidomide and its derivative, lenalidomide, are very effective when used alone in 40% of CRPS patients (23,24). Early results suggest that a combined approach will extend the beneficial results of such anesthetic and outpatient ketamine protocols.

In patients with one extremity that has not responded to these regimens, we employ somatic peripheral blocks (brachial plexus or root) with a two-day ketamine infusion (given concomitantly with the block).

Ketamine Coma Protocol

IN PATIENTS WITH A GENERALIZED DISEASE who have been refractory to all modalities of treatment, we employ ketamine in anesthetic doses. Most of these patients have failed to get relief from dorsal column stimulation and morphine pump placement, in addition to all other standard therapy. Dr. Peter Rohr and Dr. Thomas Kiefer have developed the coma protocol (25). They anesthetize patients and use 150 mg of ketamine per hour with 7 mg of midazolam per hour for five days. All patients receive the usual critical-care monitoring and awaken with no CRPS pain (allodynia, hyperalgesia, and hyperpathia). Most patients suffer the original pain that initiated CRPS. On the third day of coma, patients regain their normal sympathetic tone and lose all of the inflammatory components of the illness. Thirteen of the 40 patients have remained pain-free. One patient has been pain-free for nine years, and the others between four and six years. For the remaining patients, CRPS symptomatology has reoccurred, but not to the same degree. Booster ketamine doses have blocked further progression of CRPS, and have dramatically reduced their pain. Approximately 60% of these severe late-stage patients have dramatic relief.

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The first nine of these patients have had in-depth neuropsychological testing after ketamine coma therapy, and none have shown any deficits. There have been no serious complications, such as cardiac arrest, stroke, malignant hyperthermia, or psychosis. The complications have included pulmonary and urinary tract infections, muscle weakness, taste abnormalities, and weight loss. These usually clear in four to six weeks.

Conclusions

UNTIL RECENTLY, we have focused primarily on helping CRPS patients overcome their disability and illness. Over the last 30 years, it has become clear that CRPS is not a psychiatric illness. It is all in a patient's head, but organically. Those who have such a severe degree of pain

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that they cannot work, and claim that "nobody really understands" what is happening to them, are going to be depressed. The affective component of this pain may be worse than in many other conditions.

Now we are focusing on what we know about pain on the molecular level. We stop abnormal AMPA receptor activity, block abnormal calcium-induced cascades originating from the NMDA receptor, and block the activation of microglia and astrocytes, which diminish their secretion of proinflammatory cytokines. This approach attacks the mechanisms of the disease. We have used anticonvulsants to block aberrantly firing sodium channels on C-fiber nociceptive afferents. If we can block the maintaining injury barrage, we can dramatically decrease many aspects of CRPS. If the maintaining nociceptive block persists, it will continue to release the magnesium blockade of the NMDA receptor ion channel pore with the consequences of calcium-induced enzyme cascades. Sympathetic blocks should be used early as interruption of the sympathetic drive on nociceptive afferents is occasionally a major component of the pain process.

We don't like to use narcotics for pain, since they activate glia, which secrete inflammatory cytokines. Utilizing antidepressants for the affective component of pain also increases inhibition of pain afferents in the DH. Nonsteroidal inflammatories help to desensitize the peripheral C- and A-delta fiber terminals, while the newer agents cross the blood brain barrier and help to control central sensitization. If these interventions fail and they have in all of the patients I see, we use the described ketamine protocols, and anti-inflammatory cytokine inhibitors.

Much of the symptomatology of CRPS can now be controlled. Equally important is the restoration of quality of life for patients. They are terrified of any stimuli that will increase their pain, they don't like their bodies, they are socially isolated, they have lost all confidence in themselves, and their physicians are stymied. They have severe muscle wasting and joint and dystrophic changes. They need intensive psychiatric care, physical therapy, and vocational rehabilitation to restore their lives. There is a new beginning for a great number of our patients.

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General Anesthesia with Ketamine and Midazolam for the Treatment of Refractory Complex Regional Pain Syndrome (CRPS) [Case reports with video].

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Two cases of patients with refractory CRPS who obtained improvement in pain and function after five days of general anesthesia with ketamine and midazolam are available at: www.rsdfoundation.org/en/Ketamine_Case_Reports.htm. One of the studies is briefly described below.

A 15-year-old, 35-kg female presented with a two-year history of CRPS of the lower extremities. Despite aggressive medical management that included multiple trials of antidepressants, anticonvulsants, sympathetic nerve blocks, a trial of spinal cord stimulation, and physical therapy in a comprehensive pain management program for one month, the patient's symptoms due to CRPS became progressively worse. At that point, low dose ketamine infusions were performed on three separate occasions... During the low dose ketamine infusions, she experienced complete relief of her pain due to allodynia. The relief of pain was associated with profound amnesia. Unfortunately, each time the low dose infusion of ketamine was stopped, pain due to allodynia returned immediately to the pre-infusion level. During the course of low dose ketamine infusions, CRPS spread to the upper extremities.

The patient was admitted to the intensive care unit and central intravenous and arterial cannulae were inserted and electrocardiogram electrodes and pulse oximetry sensor were applied. The patient was intubated following a loading dose of ketamine and midazolam. The dose of ketamine and midazolam was adjusted over the five-day infusion in order to maintain adequate anesthesia.

Cardiovascular parameters were stable throughout the infusion. Upon emergence from general anesthesia, the patient developed hallucinations that were controlled with propofol and midazolam. She was discharged from the hospital three days after extubation. One month after the ketamine procedure a significant improvement in pain thresholds was noted. There was no decline in cognitive function one month following the high dose ketamine procedure based on the RBANS total score for the patient. Following the high-dose ketamine procedure, allodynia completely disappeared and the patient was able for the first time to shower, wear shoes, climb stairs, and sleep with sheets.