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REVIEW ARTICLE/BRIEF REVIEW

Update on the pathogenesis of complex regional pain syndrome: Role of oxidative stress

Mise au point sur la pathogenèse du syndrome douloureux régional complexe et le rôle du stress oxydatif

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Abstract

Purpose *Complex regional pain syndrome (CRPS) is a chronic inflammatory pain syndrome that affects one or more extremities of the body. It is characterized by burning pain and abnormalities in the sensory, motor, and autonomic nervous systems. This review illustrates how oxidative stress and nuclear factor erythroid 2-related factor (Nrf2) activation might contribute to understanding the etiopathogenesis of CRPS.*

Principal findings *The precise cause of CRPS remains unclear, and current treatments are not effective in many patients. The mechanism underlying CRPS may differ across patients and even within a single patient over time. Inflammatory and neuronal mechanisms have been suggested as key contributors to CRPS. Recent evidence demonstrates that oxidative stress is associated with clinical symptoms in patients with CRPS-I. Oxidative stress plays a key role in CRPS pathogenesis. The Nrf2 factor is a master regulator of the transcription of multiple antioxidants, which protects against oxidative stress and inflammation by inducing antioxidant and detoxifying genes through binding with an antioxidant response element. It has antinociceptive effects against inflammatory pain in an animal model.*

Conclusion *This review summarises the effect of oxidative stress and mitochondrial dysfunction in the pathogenesis of CRPS. It also addresses the question of whether there is a potential role for Nrf2 (activated by pharmacological or nutritional activators) in alleviating the clinical features of CRPS or preventing its progression.*

Résumé

Objectif *Le syndrome douloureux régional complexe (SDRC) est un syndrome de douleur inflammatoire chronique affectant un ou plusieurs membres; il est caractérisé par des douleurs de type brûlures et par des anomalies des systèmes nerveux sensitif, moteur et autonome. La cause précise du SDRC est encore inconnue et les traitements actuels sont inefficaces chez de nombreux patients. Le mécanisme sous-jacent du SDRC peut varier selon les patients et même chez un même patient au fil du temps. Des mécanismes inflammatoires et neuronaux ont été proposés comme jouant un rôle clé dans la genèse du SDRC. Les constatations tirées des études récentes montrent que le stress oxydatif est associé aux symptômes cliniques du SDRC-1. L'objectif de cet article de synthèse est d'illustrer comment le stress oxydatif et l'activation d'un facteur apparenté au facteur nucléaire érythroïde-2 (Nrf2) pourraient contribuer à la compréhension de l'étiopathogenèse du SDRC.*

Constatations principales *Le stress oxydatif joue un rôle essentiel dans la pathogenèse du SDRC. Le facteur apparenté au facteur nucléaire érythroïde-2 est le maître régulateur de la transcription de multiples antioxydants protégeant contre le stress oxydatif et l'inflammation par*

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l'induction de gènes antioxydants et détoxifiants, via une liaison avec l'élément de réponse antioxydante. Le facteur apparenté au facteur nucléaire érythroïde-2 a des effets antinociceptifs contre la douleur inflammatoire dans des modèles animaux.

Conclusion *Cet article de synthèse résume l'effet du stress oxydatif et des troubles de la fonction mitochondriale dans la pathogenèse du SDRC et recherche le rôle éventuel d'une activation du Nrf2 par des activateurs pharmacologiques ou nutritionnels sur l'amélioration des caractéristiques cliniques du SDRC ou sur la prévention de son évolution.*

Complex regional pain syndrome (CRPS) manifests as chronic inflammatory neuropathic pain, typically in the extremities after acute tissue injury of unknown etiology, although it may occur with no obvious inciting event.[1] The excruciating pain and diverse autonomic, sensory, and motor dysfunctions are disproportionate to any inciting event. Complex regional pain syndrome is subdivided into CRPS I (reflex sympathetic dystrophy) and CRPS II (causalgia), reflecting, respectively, the absence or presence of documented nerve injury.[1,2] The most common initiating events are surgery, nerve compression, fractures, tissue trauma, ischemia, and sprains.[2,3]

Based on previous evidence from clinical trials and animals studies, the general hypothesis is that CRPS is a disease of the central nervous system. The clinical picture comprises a characteristic clinical triad of symptoms including autonomic (disturbance of skin temperature, presence of sweating abnormalities in the affected region), sensory (pain, hyperalgesia), and motor (paresis, tremor, dystonia) disturbances.[3-5] Impaired microcirculation during the chronic stage of CRPS is related to increased vasoconstriction, tissue hypoxia, and metabolic acidosis of the tissues of the affected limb.[6]

Epidemiological studies indicate that there are at least 50,000 new cases of CRPS I annually in the United States.[7,8] Complex regional pain syndrome can affect both sexes and persons of all ages (including children), although it is thought to be more common between the ages of 40 and 60 yr and may be more frequent in women. The syndrome affects all aspects of daily physical functioning. It has also been reported that CRPS is associated with a particularly poor quality of life, with large health care costs. It has a negative impact on personal relationships, careers, and mental health, making it a public health issue.[9,10] Failure to diagnose a true case of CRPS has its own costs, mostly derived from excess general practitioner visits, investigations, and prescriptions.

Invasive and expensive palliative interventions—intravenous infusions (e.g., ketamine), nerve block, sympathetic block, spinal cord stimulation, peripheral nerve stimulation, implantable spinal medication pumps, chemical and surgical sympathectomy[11-18]—are often used, contributing to the high cost of treating CRPS and resulting in an enormous economic burden. Also, clinical studies have failed in various patient subtypes to demonstrate the efficacy of many of these interventions and have reported unpredictable outcomes.[13]

There are no specific pharmacological drugs approved for the treatment of CRPS, and no reliable protocol is available for use in these patients. Although traditional therapies such as physiotherapy, range of motion exercises, and pain medications (e.g., antiepilepetics, antidepressants, opioids, antiinflammatories, bisphosphonates) offer temporary relief, they have not been shown to change significantly the overall course of the syndrome[13] (Fig. 1). These poor results may be due to poor therapeutic mechanisms, the diversity of the symptoms, or diverse patient responses.

The diagnostic criteria are not yet optimized or even standardized. There is no simple, objective, noninvasive marker for monitoring disease activity or the effects of treatment.[2,12] The present diagnostic criteria for CRPS I and CRPS II depend solely on taking a meticulous history and conducting a careful physical examination. There are no specific tests (or gold standard) to confirm the diagnosis.[2,12,19] The search is on for clinically useful, noninvasive diagnostic markers to screen cases accurately. With no specific clinical symptoms, diagnosing CRPS is an emerging challenge and an important area of clinical research. Evaluating the cost-effectiveness of various noninvasive diagnostic markers and the difficulty of predicting or even observing disease activity of patients suffering from CRPS comprise a challenge for clinicians.

There is no single pathophysiological mechanism that can explain the diversity and heterogeneity of the symptoms. At the National Institutes of Health State-of-the-Science Meeting on CRPS held in December 2001 (Washington, DC), it was concluded that the existing research on the mechanisms of human CRPS is inadequate and that it has failed to capture adequately the complex nature of the condition observed clinically in patients.[19] It is not clear why CRPS develops in some patients but not in others despite similar initiating events. No clear predisposing factors have been identified.

This review summarises briefly the current findings about the CRPS mechanisms that are most widely accepted and documented in the literature. In addition, we describe the oxidative stress and mitochondrial dysfunction mechanism that we hypothesized plays a significant role in the pathogenesis of CRPS. More complete understanding of the mechanisms through which nuclear factor erythroid 2-related factor (Nrf2) confers protection against oxidant injury may lead to alternative intervention strategies for CRPS.

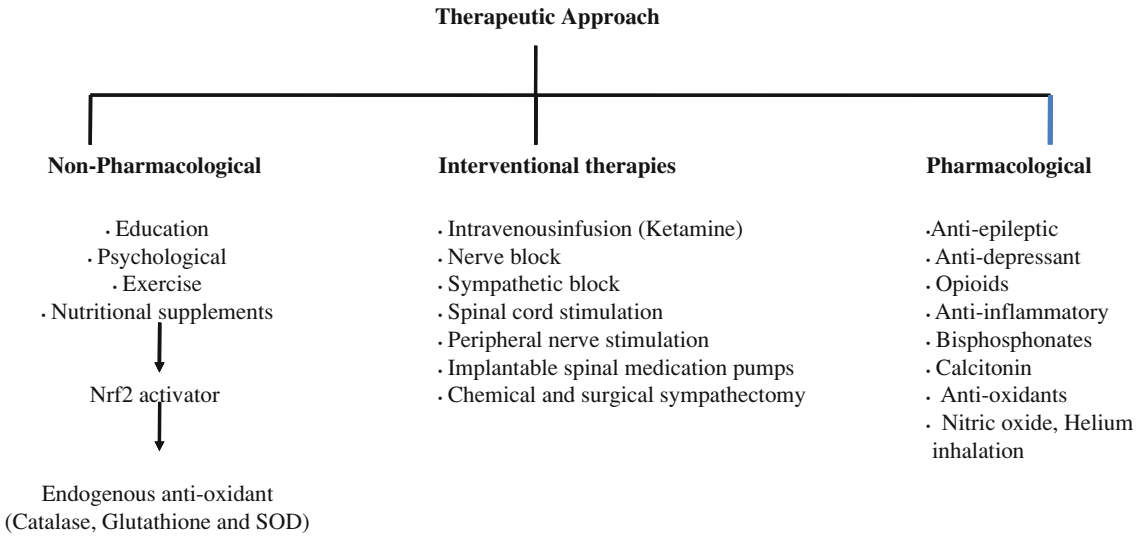

Fig. 1 Nuclear factor erythroid 2-related factor activation contributes to alleviating the effects of the complex regional pain syndrome (CRPS). Traditional therapies are physiotherapy, range of motion exercises, and pain medications (e.g., antiepileptics, antidepressants, opioids, antiinflammatories, bisphosphonates). Invasive interventions include intravenous infusion (e.g., ketamine), nerve block, sympathetic block, spinal cord stimulation, peripheral nerve stimulation, implantable spinal medication pumps, and chemical and surgical sympathectomy. Nuclear factor erythroid 2-related factor confers protection against oxidant injury, which may lead to alternative intervention strategies for treating CRPS

Inflammation contributes to CRPS pathogenesis

Several theories about disease mechanisms for CRPS have been offered in the literature, but most questions addressing mechanisms clearly remain open. It has been suggested that enhanced peripheral neuronal inflammation, local and classic systemic inflammation, sympathetic nervous system dysfunction, and central nervous system abnormality are major mechanisms that contribute to the pathogenesis of CRPS in a genetically susceptible individual.[19-21] In fact, genetic predisposition and environmental stress are key factors in CRPS development and may explain the increased vulnerability of some individuals (Fig. 2). Studies examining familial CRPS occurrence patterns indirectly support a genetic contribution and provide support for the possibility that CRPS is heritable in some cases.[22]

There is evidence demonstrating that neurogenic inflammation and activation of the immune system contributes to CRPS mechanisms.[23,24] It has been observed that an increased systemic level of calcitonin gene-related peptide in patients with CRPS plays a significant role in its pathogenesis.[23] Other work indicates that plasma bradykinin levels are significantly higher in CRPS patients than in healthy controls.[24]

It has also been observed that corticosteroids significantly diminished the clinical features of CRPS, indicating that inflammatory mechanisms might evolve into CRPS.[25] Furthermore, several small clinical studies demonstrated that, compared with controls and non-CRPS pain patients, CRPS patients display significant increases in proinflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumour necrosis factor α (TNFα), and a decrease in antiinflammatory factors, including IL-10 cytokines in local blister fluid, circulating plasma, and cerebrospinal fluid.[26,27] Interestingly, administration of a TNFα antibody reduces CRPS symptoms in some patients.[28] Further research on TNFα therapy as a cost-effective treatment option for this disease is needed.

During chronic inflammation, activated immune cells generate reactive oxygen species (ROS), which subsequently produce oxidative injury along with a concomitant imbalance in redox status. Generation of ROS is an important factor in maintaining inflammation. Activation of inflammatory cells can, in turn, generate ROS, leading to a vicious circle of excessive oxidative stress production.

Definition and role of oxidative stress in CRPS pathogenesis

Oxidative stress has been involved in a number of diseases, including cardiac, respiratory, neurodegenerative, and gastrointestinal diseases and cancer; and it has been associated with aging and pain.[29,30] Oxidative stress results from an imbalance between ROS production and antioxidant defence. The most important free radicals are oxygen derivatives—particularly superoxide anion (O_2–•), hydroxyl radical (OH–), and hydrogen peroxide (H_2O_2)—and reactive nitrogen species such as nitric oxide and peroxynitrite.[31,32]

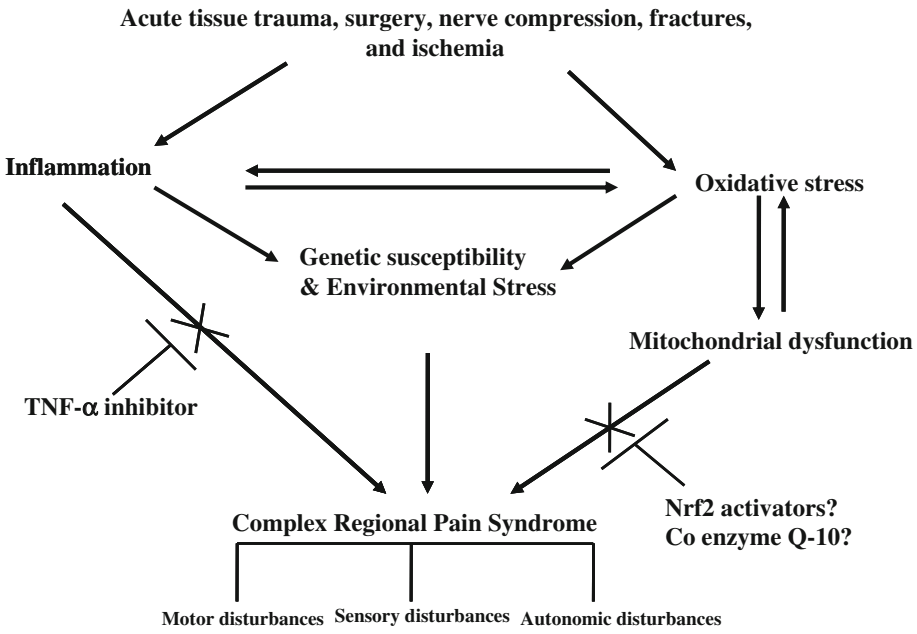

Fig. 2 Proposed hypothesis. Oxidative stress is a major mechanism involved in the pathogenesis of CRPS in genetically susceptible individuals. Activation of nuclear factor erythroid 2-related factor (Nrf2) may contribute to diminishing the effects of CRPS via various cytoprotective functions, mainly its antioxidant and antiinflammatory effects

Under normal physiological conditions, a number of endogenous biological mechanisms are present that counteract changes in redox balance, including superoxide dismutase (SOD), catalase, and other antioxidant enzymes. Activation of antioxidant systems inhibits radical generation and terminates oxidative processes. However, an increase in ROS formation to a pathological level for a certain duration can overwhelm the antioxidant defence and affect cell functions.

Antioxidants are produced in the body but can also be extracted from foods such as fruits, vegetables, seeds, nuts, meats, and oil.[29,30] There are two types of antioxidant defence within the cell. The fat-soluble antioxidant consists of vitamin E, β-carotene, and coenzyme Q.[10] The cell's water-soluble antioxidants include vitamin C, glutathione peroxidase, SOD, and catalase.[30-33]

It has been speculated that free radical generation by the mitochondrial respiratory chain contributes to the pathophysiology of CRPS I.[34-36] Eisenberg *et al*. demonstrated significant increases in malondialdehyde, lactic dehydrogenase, and antioxidants (peroxidase, superoxide dismutase, uric acid) in the serum and especially the saliva of CRPS I patients compared to healthy controls.[34] Furthermore, Coderre *et al.* detected elevated levels of malondialdehyde in the hind paw muscles of the rat and have shown that the animal's pain hypersensitivity is reduced by free radical scavengers and antioxidant therapy.[35,36] Taken together with the previous data, we observed that oxidative stress occurs mainly in CRPS I. Although previous clinical studies have indicated the presence of oxidative stress in CRPS I patients, it has been difficult to prove whether it is a cause or a consequence of CRPS I.

Supporting the oxidative stress hypothesis, it has been observed that vitamin C as an antioxidant reduces the prevalence of CRPS in humans after wrist fractures. A daily dose of 500 mg for 50 days was recommended.[37] Furthermore, the effectiveness of vitamin C in preventing CRPS I of the foot and ankle—a frequent complication after trauma—has been demonstrated.[38,39] Commonly used antioxidants have proved effective in clinical trials on various oxidative-related human diseases (e.g., hypertension).[40]

As the mitochondrion is the major source of ROS,[41] it is reasonable to speculate that mitochondrial dysfunction related to oxidative stress might play a role in the pathogenesis of CRPS. Mitochondrial dysfunction has been recognized as an important inducer to an array of human pathologies, including neurodegeneration, diabetes, and ischemia-reperfusion injury.[42]

Tan *et al*. observed that mitochondria obtained from CRPS-I muscle tissue displayed reduced mitochondrial ATP production and substrate oxidation rates in comparison to control muscle tissue, suggesting that reduced mitochondrial energy production combined with ROS induced damage in muscle tissue from CRPS I patients.[43] Tan *et al*. also demonstrated that ROS evoked damage to mitochondrial proteins and reduced manganese sodium dismutase (Mn SOD) levels. It has also been observed that venous oxygen saturation is significantly increased in patients with chronic end-stage CRPS I, in correspondence with impaired oxygen diffusion related to mitochondrial dysfunction.[44] Prospective studies are needed to test our hypothesis comprehensively that oxidative stress contributes to CRPS development in humans. The key questions raised are whether mitochondrial dysfunction plays a primary role or is a consequence of the pathogenesis of CRPS.

Mitochondria are becoming promising targets for drug discovery and therapeutic interventions. In recent years, scientific interest has focused increasingly on molecules to inhibit ROS-mediated damage, activation of endogenous antioxidant enzymes via activation of nuclear transcription factors such as Nrf2, and administration of mitochondria-targeted antioxidants such as Mito-Vitamin E and Mito-coenzyme Q.[45] However, research on mitochondria-targeted antioxidants is still in its infancy, and much more time is needed to develop more reliable data. The importance of our speculation might be that it provides opportunities to develop novel therapeutic interventions that improve mitochondrial function and that may slow the progression of CRPS processes.

Role and clinical implication of nuclear-related factor in CRPS

Nuclear factor erythroid 2-related factor is a basic leucine-zipper motif transcription factor that heterodimerically binds the antioxidant-responsive element (ARE) in the promoter regions of many cytoprotective genes. Nuclear factor erythroid 2-related factor is activated in response to an increase in ROS and tries to stabilize the redox hemostasis by transcribing antioxidant genes. It has also been observed that it has various cytoprotective functions, mainly as an antioxidant and an antiinflammatory agent.[46,47]

At the present time, there is no proof directly linking Nrf2 to the CRPS mechanism. However, taking the Nrf2 multifunction protection phenomenon into consideration—with Nrf2 coordinately up-regulating antioxidant and antiinflammatory genes and cell type-specific genes that are required for the defense system—we suggest that suboptimal Nrf2 activity may be involved in a subgroup of CRPS patients. Our hypothesis needs to be tested using a multidisciplinary approach, which includes clinical experimentation in human models. Further studies are therefore needed to examine Nrf2 transcripts in other susceptible populations, with the possibility that it may have beneficial effects.

Nuclear factor erythroid 2-related factor signaling has become an attractive target and promising approach for prevention and treatment of many oxidative stress-related diseases.[48,49] Activators of Nrf2 are widely available and have proved to be well tolerated; furthermore, they have the ability to cross the blood–brain barrier. Over the last few decades, numerous Nrf2 activators have been developed, and some are currently undergoing clinical trials.[50] They include endogenous activators (e.g., ROS, lipid aldehydes) and exogenous agents (e.g., heavy metals, electropholic xenobiotics).[51] Some nutraceutical compounds are also activators of Nrf2 (e.g., sulforaphane, curcumin, resveratrol, caffeic acid phenyl ester, tocopherol).[49,50] Sulforaphane, an isothiocyanate compound present in high concentrations in broccoli sprouts and other crucifers, was found to be a potent inducer of the Nrf2-regulated cytoprotective adaptive response. Certain chemopreventive agents and synthetic antioxidants (e.g., ethoxyquin, oltipraz, phorbol esters) also play a role in Nrf2 activation.[49,52,53] The chemopreventive potential of oltipraz appears to be related to the up-regulation of Nrf2 on carcinogen metabolism in humans.

Numerous *in vivo* studies have illustrated that Nrf2 plays an important role in modulating inflammation in a variety of experimental models.[53-55] It has been proposed that Nrf2 modulates inflammation by inhibiting the NF-κB pathway, thereby maintaining redox homeostasis. de Mos *et al.* demonstrated that NF-κB plays a potential role in chronic postischemia pain in an animal model in which the symptoms mimics those of CRPS I.[56]

Nuclear factor erythroid 2-related factor promises to be an attractive therapeutic target for intervention and prevention strategies for multiple chronic inflammatory diseases. Recently, Marzec *et al.* identified a number of single nucleotide polymorphisms in the promoter region of *Nrf2* in humans across multiple ethnic groups.[57] It has been suggested that polymorphisms of Nrf2-regulated genes may be useful markers of susceptibility to asthma and gastric cancer.[58]

Smith *et al.* proposed that Nrf2 polymorphisms may occur in a subtype of patients with CRPS and may contribute to factors that make these patients more susceptible to developing CRPS than the general population.[59] It will be worthwhile to do more advanced genetic and molecular biology testing to investigate the potential role of Nrf2 in the pathogenesis of subpopulations with CRPS and to determine if it is involved in the onset and activity of diseases. Identification of biomarkers that define disease subtypes can be of real value when designing specific therapies. Nrf2 genetic variation could potentially be used to identify at-risk individuals (e.g., trauma patients) for pharmacogenomic prevention trials. Future investigations will be instrumental in confirming these observations.

Future directions and conclusions

Mechanism-based treatment has long been a goal in CRPS management, and further understanding of its pathophysiology may eventually permit that goal to be achieved. Understanding the pathways by which oxidative stress influences CRPS can help us better understand the biological mechanisms of its pathogenesis, eventually leading to the discovery of better therapies.

There are several areas that still need to be explored. Among them is the development of noninvasive explicit or surrogate biomarkers of CRPS pathogenesis. Such biomarkers would also be useful in assessing the effectiveness of therapeutic interventions. Additional work is needed to determine the extent to which the various available animal models of CRPS successfully mirror clinical features and mechanisms underlying human CRPS. The availability of new animal models that closely resemble the human disease is expected to allow further characterization of the initiating events in CRPS and may lead to a possible cure for this devastating disease.

If our hypothesis (or speculation) that CRPS is an oxidative-inflammatory syndrome is proven in large clinical studies, it would clear the way to test Nrf2 in CRPS patients. Future investigations might appropriately focus on the role of Nrf2 as an antiinflammatory and antioxidant agent and establish that it is involved in mitochondrial function; it could then be used as a mediator of pain. Studies on the discovery and testing of mitochondria-targeted drugs promise to play a critical role in the search for new, targeted therapeutic approaches.

It seems that pain medications are associated with measurable effects on some aspect of mitochondrial function, although causal relations are difficult to establish. Much work remains to be done regarding Nrf2 activation in clinical research focussing on pain mechanisms and suppression of inflammation. Our hypothesis raises a few questions without answers as yet. Undoubtedly, future research should address several outstanding questions remaining to be elucidated, which include the following.

1. Does Nrf2 activity contribute to the motor, sensory, and autonomic disturbances seen in patients with CRPS?
2. Can Nrf2 generation by pharmacological or nutritional inducers be manipulated in a safe manner to help ameliorate CRPS or other inflammatory pain syndromes? Might the future target be a gene?
3. Dose Nrf2 activity correlate with disease onset, duration, and severity?

It is our sincere hope that further identification and clarification of the specific gene(s) involved in CRPS will help in the development of new classes of drugs and therapeutic options.

Competing interests None declared.

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