Targeting Neuroprotection as an Alternative Approach to Preventing and Treating Neuropathic Pain

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Summary: Neuropathic pain syndromes arise from dysfunction of the nerve itself, through traumatic or nontraumatic injury. Unlike acute pain syndromes, the pain is long-lasting and does not respond to common analgesic therapies. Drugs that disrupt nerve conduction and transmission or central sensitization, currently the only effective treatments, are only modestly effective for a portion of the patients suffering from neuropathic pain and come with the cost of serious adverse effects. Neurodegeneration, as a reaction to nerve trauma or chronic metabolic or chemical intoxication, appears to be an underlying cause of neuropathic pain. Identifying mechanisms of neurodegeneration and designing neuroprotective therapies is an ambitious goal toward treating or even preventing the development of these disabling disorders. **Key Words:** Neuropathic pain, neurodegeneration, trophic factors, mitochondria.

INTRODUCTION

Although unpleasant, acute or transient pain after traumatic injury, surgery, sunburn, or secondary to inflammation usually resolves spontaneously. In the meantime, the pain can be relieved by local anesthetics, anti-inflammatory drugs, or, in the most severe cases, temporary use of mild to strong opiates. In contrast, in addition to traumatic nerve injury (including stroke and spinal cord damage), some chronic diseases such as diabetes, HIV, and varicella zoster infection are associated with a high probability of developing neuropathic pain. In some cases, painful neuropathy may be due to nerve damage caused by the disease itself, or it may develop as an iatrogenic artifact of the treatment. For example, repeated rounds of chemotherapy with microtubule targeting agents or platins and long-term use of HIV-controlling antiretroviral drugs often result in painful neuropathy.[1] Nerve damage or dysfunction can be demonstrated in these and a number of other syndromes that are associated with chronic pain (e.g., multiple sclerosis), leading to the hypothesis that chronic or neuropathic pain is a symptom of neurodegeneration.

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The neurodegeneration may be subtle or undetectable as measured by histological methods, but even without overt signs of neuronal cell death or axon degeneration, neuronal dysfunction can be detected by changes in neural excitability and conduction parameters or gene and protein expression. These changes, as well as loss of specific nerve populations, perturb the coordinated signaling that is important for interpreting sensory stimulation. Peripheral nerve damage or dysfunction can be expected to result in alterations in both neuronal conduction and transmission to those centers that integrate and interpret sensory stimulation. It stands to reason that these painful conditions may respond only to drugs, such as anticonvulsants and anesthetics, that interrupt neuronal conduction or transmission, or to antidepressants, which may normalize central processing of sensory information. Although drugs in these classes have shown modest efficacy and are approved for the treatment of some forms of neuropathic pain, how they work is still far from clear.

Nonetheless, if neurodegeneration is the underlying cause of neuropathic pain, it seems logical to consider neuroprotection as a means either to prevent the onset, control progression or even to reverse the nerve damage leading to these chronic pain syndromes. Neuroprotection would consist of methods that maintain neuronal survival or function in the face of a pathological stress. This stress could include systemic neurotoxic insults

caused by metabolic disorders or drugs, as well as the effect of nerve damage on otherwise uninjured neighboring neurons.

This review addresses some types of neuropathic pain that may be amenable to neuroprotective approaches. It is speculative regarding the role that neurodegeneration plays in these painful and troubling symptoms and, although far from exhaustive, provides some selected instructive examples that may provoke thoughts on the medical challenge to finding effective treatments of neuropathic pain by targeting neuroprotection.

PAIN CONDITIONS ASSOCIATED WITH NEURODEGENERATION AND POSSIBLE CAUSES

Diabetes

Most persons with diabetes will develop some degree of peripheral neuropathy, starting a decade or more after disease onset, and 10–30% will develop neuropathic pain. A recent study of the prevalence and severity of painful neuropathy in type 2 diabetic patients found that 24% have neuropathic pain, and more than 75% consider their pain moderate or severe according to established neurological and pain scales.[2]

Hyperglycemia with resulting oxidative stress is the underlying cause of the neurovascular complications of diabetes and is the major risk factor for both neuropathy and neuropathic pain.[3–5] Indeed, the interdependence of nerves and blood vessels leads to a vicious cycle in which changes in the vasculature that result in increased vasoconstriction restrict nutrient and oxygen supply to the nerves, leading to dysregulation of nerve input to the vasculature. High intracellular glucose favors glycolysis and the polyol cycle, both leading to an increased supply of the reduced agents NADH (nicotinamide adenine dinucleotide reduced form) and $FADH_2$ (flavin adenine dinucleotide reduced form). Excess accumulation of these electron donors can then lead to overproduction of reactive oxygen species by the mitochondrial electron transport chain. Excess glucose can also be covalently attached to proteins producing age-related glycation endproducts, and receptors for these endproducts can also contribute to oxidative stress. Reduced supply of neurotrophic factors from surrounding tissue also increases neuronal oxidative damage.

Various therapeutic strategies targeting oxidative stress include treatment with antioxidants such α-lipoic acid or vitamins E and C, aldose reductase inhibitors, and inhibitors of age-related glycation endproduct formation or its receptors. Despite some promising results in small clinical trials, however, long-term studies have failed because of lack of efficacy or because of adverse effects (see the review by Vincent et al.[3]). Mitochondrial dysfunction induced by oxidative stress may be a major culprit in the development of neuropathy and neuropathic pain in chronic diabetes.[4]

HIV and antiretroviral therapies

Painful sensory neuropathy has become the most common neurological complication of infection with human immunodeficiency virus type 1 (HIV-1).[6] Distal sensory polyneuropathy (DSP) is directly caused by HIV-1 infection, and its severity is associated with advancing immunosuppression (low CD4 cell count) and viral load.[7,8] Antiretroviral toxic neuropathy (ATN) resulted from the neurotoxicity of components of highly active antiretroviral therapy (HAART).[9,10] Both DSP and ATN share similar clinical features, including burning pain and symmetrical paresthesias. Both are characterized by a dying back axonal degeneration of long axons in distal regions, loss of unmyelinated fibers, and reduced intraepidermal nerve fiber density that correlates with disease severity and progression.[11–13]

Among HAART components, dideoxynucleoside reverse transcriptase inhibitors (NRTIs, mainly didanosine [ddI], and stavudine, or d4T) were significantly associated with a heightened risk for symptomatic ATN[14]; however, a combination with immune-mediated mechanisms triggered by HIV infection seems to be critical in the development of their neurotoxicity. Indeed, high doses of NRTIs are not sufficient to induce ATN in mice, and similar doses in transgenic mice for HIV coat protein gp120 induced distal degeneration of unmyelinated sensory axons.[15] Whether protease inhibitors have to be considered as a risk factor for ATN is still controversial. Neurotoxicity of indinavir was demonstrated *in vitro* on dorsal root ganglia (DRG) cultures, and an increased risk for ATN was reported with exposure to indinavir in two independent studies.[10,16] Nonetheless, evaluation of protease inhibitors as an independent risk factor for ATN in a larger cohort (1159 HIV-infected individuals) did not confirm their toxicity, except for amprenavir and lopinavir, which may slightly increase the risk for ATN.[17] Finally. the increase in survival of HIV-infected patients with prolonged medication exposure is associated with an increased risk of neuropathy.[13,16]

The pathogenesis of ATN remains poorly understood, although mitochondrial toxicity of NRTIs has been known for many years, based on their inhibition of the mitochondrial DNA polymerase-γ.[18] Indeed, increased numbers of abnormal mitochondria in nerves and significantly reduced cellular mtDNA content were evidenced in patients treated with ddC (zalcitabine).[19] Beyond inhibition of the mitochondrial DNA polymerase-γ, NRTIs have direct effect on mitochondrial membrane potential inducing energy failure and subsequent axonal degeneration in DRG cultures without neuronal loss.[20,21] Their toxicity could be even aggravated by pre-existing HIV-mediated mitochondrial defects.[22] Using feline immu-

nodeficiency virus (FIV)-infected animals, Zhu et al.[21] demonstrated that treatment with ddI exacerbated FIV neurotoxic effects, increasing pain sensation and reducing epidermal density of nerve endings. Development of ATN induced by ddI was also associated with mitochondrial injury on neurons and reduced brain-derived neurotrophic factor (BDNF) production by Schwann cells in DRGs of FIV-infected animals. Given that BDNF improves mitochondrial function, modulation of its expression may be part of the pathogenesis of ATN.[23,24]

Altogether, preclinical and clinical data highlight the convergent pathogenic effects of HIV infection and antiretroviral drugs to mediate distal axonal degeneration and pain. More than cell death at the neuronal level, local changes at the axonal level such as mitochondrial dysfunction or changes in neurotrophic factors expression may play a major role in the pathogenesis of DSP and ATN.

Chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is the main dose-limiting adverse effect of commonly used chemotherapeutic agents, including platinum drugs, taxanes, epothilones, and vinca alkaloids, but also of newer agents such as bortezomib and lenalidamide.[25] The degree and type of peripheral neuropathy depends on the chemotherapy drug, with incidence ranging from 10% to 90% of patients, and with platinum drugs such as oxaliplatin being the most toxic.[26]

For most drugs the risk increases with cumulative dose. Typically, the clinical presentation reflects an axonal peripheral neuropathy with glove-and-stocking distribution sensory loss, combined with features suggestive of nerve hyperexcitability, including paresthesia, dysesthesia, and pain. Most of the time, peripheral neuropathy reverses if the drug dose is reduced or if the treatment is stopped; however, in some cases recovery from symptoms is incomplete, and a long period of regeneration is required to restore function.[27] To date, no drug is available to reliably prevent or cure CIPN. Furthermore, recently approved drugs for treatment of diabetic neuropathic pain, such as gabapentin and pregabalin, provided no benefit in CIPN, suggesting the involvement of specific disease mechanisms.[28]

The mechanisms underlying CIPN are diverse and depend on the drug. Platinum agents (cisplatin, oxaliplatin, carboplatin) induce neuronal apoptosis in the DRG through the formation of DNA–platinum complexes and early p38 and ERK1/2 activation.[29,30] Recently, James et al.[31] also reported that cisplatin induced neurite degeneration of primary rat neurons in line with the observed axonal neuropathy in patients. Notably, the neurotoxicity of cisplatin can be alleviated by inhibiting the Rho signaling pathway.

The toxicity profile of oxaliplatin differs from those of other platinum compounds; it induces an acute neurotoxicity characterized by a rapid onset of cold-induced distal dysesthesia, followed by a chronic sensory peripheral neuropathy when treatment is continued.[32] Recently, the acute neurotoxicity of oxaliplatin was associated with its interference with neuron voltage-gated sodium channels through one of its metabolites, oxalate, a calcium chelator.[33–35]

Microtubule-targeting agents (e.g., paclitaxel, vincristine) display axonal toxicity, with the longest axons being the first affected.[36] For paclitaxel, studies in animal models using high doses initially supported the hypothesis that the drug's neurotoxicity arises from disruption of microtubules and impairment of axonal transport, but numerous reports now refute this idea.[37–40] Indeed, low doses of paclitaxel caused allodynia and hyperalgesia in rats without inducing degeneration of myelinated and unmyelinated axons in the sciatic nerve and roots.[41,42] Degeneration was rather confined to receptor terminals of the sensory fiber in the skin and was associated with prominent activation of cutaneous Langerhans cells.[43] The earliest defect observed in both C-fibers and myelinated axons was the appearance of swollen and vacuolated mitochondria.[42] In addition, these mitochondrial changes resolved when pain behavior decreased, suggesting that abnormalities in axonal mitochondria directly contribute to peripheral neuropathy and pain. Similarly, peripheral nerve biopsies from patients with vincristine-evoked painful neuropathy revealed axonal and mitochondrial swelling, whereas microtubule alterations were not evidenced.[44] Such results are in agreement with the reported mitochondrial toxicity of microtubule-targeting drugs in human cell lines, and strongly argue in favor of energy failure as the main cause of nerve hyperexcitability and degeneration observed in paclitaxel-induced peripheral neuropathy.[45,46]

Postherpetic neuralgia

Postherpetic neuralgia (PHN) is a neuropathic pain syndrome triggered by peripheral nerve damage due to reactivation of latent varicella zoster virus in sensory nerve cell bodies. The reactivated virus moves to the skin via afferent nerve fibers and may also enter nerve fibers projecting to the spinal cord. The PHN syndrome is defined as pain persisting for 3 or more months after onset of the skin rash; it can occur in up to 50% of patients, depending on age.[47,48] The pain, which is usually localized to zoster-infected areas of the skin, can include constant, deep-burning pain, brief recurrent shooting or shock-like pain, and tactile allodynia.[49] Allodynia can exist in the presence or absence of sensory loss.[50]

Although the condition stems from varicella zoster virus damage to peripheral nerves, central sensitization

also plays an important role in PHN. Peripheral and central demyelination may be implicated, as well as nerve damage. As in other types of nerve injury, changes in the expression or activation of voltage-dependent sodium channels and NMDA receptors may underlie sensory nerve hyperexcitability and central sensitization, respectively. (Note that, although neuroprotection is the subject of this review, recent clinical trials suggest the opposite approach: using high-concentration topical capsaicin to ablate sensory nerve terminals offers an effective treatment for PHN.[51]) Ultimately, neuroprotection will be afforded by preventing PHN through vaccination against herpes zoster virus.[52,53]

Multiple sclerosis

According to the National Multiple Sclerosis Society (http://www.nationalmssociety.org), almost half of all people with multiple sclerosis (MS) are troubled by chronic pain, which can include acute burning, tingling, shooting, or stabbing pain, trigeminal neuralgia, L'Hermitte's sign (a brief, stabbing, electric-shock-like sensation running down the spine brought on by bending the head forward), or dysesthesia, a burning, aching, or girdling around the body. In MS, pain originates mainly from damage in the CNS and shares similarities with central pain caused by stroke and spinal cord injury.[54–56] Mechanisms underlying central pain are still largely unknown but lesions affecting the spinothalamo-cortical track appear as a risk factor for developing central pain.[57,58] Although all approved treatments for MS attempt to reduce the inflammatory, autoimmune process that destroys central myelin, they do little to halt the progression of the disease, which is due to degeneration of demyelinated axons. Neuroprotective therapies are badly needed, either to directly prevent axon and nerve degeneration or to stimulate remyelination.[59,60]

NEURODEGENERATION: MECHANISMS & POSSIBLE TARGETS

Trophic factors: pros and cons

If neuropathic pain is a consequence of neurodegeneration, then neurotrophic factors could provide a neuroprotective strategy. The role and regulation of the major neurotrophic factors implicated in neuropathy and pain (nerve growth factor, NGF; BDNF; neurotrophin 3, NT3; and glial cell line-derived neurotrophic factor, GDNF), and their receptors, have been thoroughly reviewed.[61]

NGF and its receptor, neurotrophic tyrosine kinase type 1 (TrkA), are required for the development of sympathetic and sensory neurons, and reduced levels of NGF are implicated in diabetic and chemotherapy-induced neuropathy. NGF administration can prevent development of neuropathy and reduction in pain thresholds in animal models of diabetic and chemotherapy-induced neuropathic pain. However, increased expression and release of NGF is one mechanism underlying inflammatory pain, and administration of NGF to naïve animals lowers pain thresholds. NGF-induced hyperalgesia may be due to its ability to induce expression of BDNF and neuromediators such as calcitonin gene-related peptide (CGRP) and substance P. NGF and TrkA signaling also increases expression, activation properties, or axonal distribution of sodium channels in DRG neurons. Indeed, BDNF signaling through TrkB is involved in central sensitization in chronic pain states and has recently been shown to be required for the establishment of persistent pain states (but not for acute pain responses).[62] Although NGF may be beneficial for treating or preventing neuropathy, it appears to be contraindicated for reversing pain. In fact, clinical trials of NGF in patients with diabetic neuropathy and HIV-induced neuropathy either failed to provide sufficient evidence of efficacy or resulted in painful adverse effects (Table 1).

Paradoxically, strategies to antagonize NGF using neutralizing antibodies, soluble TrkA receptors, or TrkA antagonists are also being considered for the treatment of chronic pain.[63] In contrast to BDNF and NGF, GDNF appears to have generally beneficial effects in animal models of nerve injury-induced painful neuropathy, without producing hyper or hypoalgesia in naïve animals. The GDNF family of trophic factors and their receptors (the receptor tyrosine kinase RET in combination with a family of GPI-linked coreceptors) are widely expressed in the central and peripheral nervous system. Targeting those expressed in DRG nociceptors (artemin and RET-GRFα3) may be a future strategy for treating painful neuropathies.[64]

Excitotoxicity: not just glutamate

Excitotoxicity most commonly refers to glutamate-induced neurotoxicity mediated by ligand-gated ion channels, particularly those permeable to calcium. Glutamate receptors, and NMDA receptors in particular, may be involved in central sensitization to peripheral hyperexcitability.[65] Although glutamate receptors would be relevant targets for both neuroprotection and symptomatic pain relief, they are widely distributed in the nervous system, and antagonists have cognitive and psychotomimetic effects.[66]

In addition to glutamate receptors, other ion channels may also play a role in excitotoxicity leading to axon and nerve terminal degradation. TRPV1 (transient receptor potential cation channel, subfamily V, member 1) receptors are heat-activated nonselective cation channels expressed on sensory nerve endings; they transduce burning pain when activated by capsaicin, a compound found in chili peppers.[67] Chronic activation of TRPV1 receptors by capsaicin leads to calcium overload and degen-

Table 1. *Neuroprotective Agents Explored or Still in Clinical Development for Treating Peripheral Neuropathies with Documented Results or Listed at ClinicalTrials.gov*

Compounds and Trials	Company	Latest Development Status	Mechanism
Recombinant human nerve growth factor (rhNGF)	**Genentech and clinician-sponsored**	**Phase III; stopped**	**Neurotrophic factor**
A randomized trial in 1019 diabetic patients to receive either rhNGF or placebo for 48 weeks failed to confirm the earlier indications of efficacy.[148] NCT00000842: A Phase II, Double-Blind Trial of Recombinant Human Nerve Growth Factor for Treatment of HIV-Associated Sensory Neuropathy. Failed to demonstrate efficacy of NGF; painful adverse effects were dose limiting for NGF.[149]			
Recombinant human brain derived neurotrophic factor (rhBDNF)	**Genentech**	**Phase II; no recent update**	**Neurotrophic factor**
A double-blind placebo-controlled clinical trial of recombinant human brain-derived neurotrophic factor (rhBDNF) in diabetic polyneuropathy (30 patients): some improvement in cool detection threshold when compared with baseline.[150]			
PROCRIT (epoietin alfa; recombinant human erythropoietin)	**Johnson & Johnson Pharmaceutical**	**Phase II**	**Neurotrophic factor**
NCT00267007: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, 18 Week Pilot Study to Investigate the Neuroprotective Effect of PROCRIT (Epoetin Alfa) on the Development of Peripheral Neuropathy in Patients Receiving Combination Taxane and Platinum-Based Chemotherapy for Cancer (33 patients); study terminated because of slow recruitment.			
prosaptide	**Savient Pharmaceuticals**	**Phase II; stopped**	**Neurotrophic factor**
NCT00286377: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Dose Ranging Study to Evaluate the Efficacy and Safety of Prosaptide Over 6 Weeks of Treatment for the Relief of Neuropathic Pain Associated With HIV-1 (350 patients); completed; not effective.[151]			
Leteprinim potassium (Neotrofin, AIT-082, SPI-205)	**Spectrum Pharmaceuticals/NeoTherapeutics**	**Phase II; no recent update**	**Neurotrophin enhancer**
NCT00041795: A Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study of Neotrofin to Treat Patients With Sensory or Motor Neuropathy Caused by Chemotherapy for Cancer (50 patients); completed; no published results.			
Xaliproden (SR57746A)	**Sanofi-Aventis**	**Phase III; active**	**Neurotrophin enhancer**
NCT00272051: A Multicenter Randomized Double-Blind Placebo Controlled Phase III Study of the Efficacy of Xaliproden in Reducing the Neurotoxicity of the Oxaliplatin and 5-FU/LV Combination in First-Line Treatment of Patients With Metastatic Colorectal Carcinoma (MCRC) (620 patients). An overall CIPN rate of 73–74% was reported in the two groups, with a lower incidence of grade 3 CIPN, 17% vs 11%, favoring the xaliproden arm; however, xaliproden did not reduce the overall incidence of neurotoxicity, but rather shifted 5% of patients from grade 3 to grade 2 of neurotoxicity. The use of xaliproden in this trial was not associated with a higher cumulative oxaliplatin dose or a longer time on therapy.[138] NCT00305188: A Multicenter, Randomized Double-Blind Placebo Controlled Phase III Study of the Efficacy of Xaliproden in Preventing the Neurotoxicity of Oxaliplatin in First-Line Treatment of Patients With Metastatic Colorectal Cancer Treated With Oxaliplatin/5-FU/LV (900 patients); active not recruiting; results end 2009. NCT00603577: A Multi-Center, Randomized, Double Blind, Placebo Controlled Phase III Study to Assess the Efficacy of Xaliproden in Patients With Oxaliplatin-Induced Peripheral Sensory Neuropathy (PSN) Following Adjuvant Chemotherapy for Colon Cancer (244 patients); active and recruiting; results end 2010.			

(*Table continues*)

Table 1. *Continued*

Compounds and Trials	Company	Latest Development Status	Mechanism
MCC-257	**Mitsubishi Pharma**	**Phase II; no recent update**	**Neurotrophin enhancer**
NCT00307749: A Phase II, Randomized, Double-Blind, Placebo-Controlled, 24-Week Dose Finding Study to Evaluate the Efficacy and Safety of 20 mg, 40 mg and 80 mg of MCC-257 in Patients With Mild to Moderate Diabetic Polyneuropathy (420 patients); completed; no published results.			
TAK-128	**Takeda/Mitsubishi Pharma**	**Phase II; stopped**	**Myelin formation accelerator**
NCT00756041: an Open-Label, Multi-Center Study to Evaluate the Safety of Long-Term Administration of TAK-128 in Subjects With Mild to Moderate Diabetic Peripheral Neuropathy (221 patients); completed; lack of efficacy. NCT00229437: A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of Three Doses of TAK-128 in Subjects With Mild to Moderate Diabetic Peripheral Neuropathy (343 patients); completed; no published results.			
SSR180575	**Sanofi-Aventis**	**Phase II; completed/stopped**	**PBR ligand**
NCT00502515: A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study of the Effect of SSR180575 at Two Doses for 24 Weeks Treatment on the Rate of Regeneration of Epidermal Nerve Fibers in Patients With Mild Diabetic Peripheral Neuropathy (270 patients); completed; results 2009.			
Thioctic acid (alpha-lipoic acid)	**MEDA Pharma and clinician-sponsored**	**Phase III; active**	**antioxidant**
Diabetic polyneuropathy; a 2-year multicenter randomized double-blind placebo-controlled trial (ALADIN II); some improvements in nerve conduction in a subset of patients.[152] NCT00328601: Assessment of Efficacy and Safety of Thioctic Acid in the Oral Treatment of Symptomatic Diabetic Neuropathy (SYDNEY 2) Randomised, Double-Blind, Placebo-Controlled Multicentre Trial With 4 Parallel Groups (170 patients); completed. Oral treatment with alpha-lipoic acid for 5 weeks improved neuropathic symptoms and deficits in patients with diabetic polyneuropathy. An oral dose of 600 mg once daily appears to provide the optimum risk-to-benefit ratio.[153] NCT00477607: Prevention of Cisplatin Ototoxicity with the Antioxidant Alpha-Lipoic Acid; under recruitment. NCT00112996 & NCT00705029: Prevention of Cisplatin- or Oxaliplatin-Induced Peripheral Neuropathy with Alpha-Lipoic Acid: A Placebo-Controlled Phase III Trial; under recruitment. NCT00079807: Painful HIV Neuropathy: Treatment With Alpha-Lipoic Acid. A phase II placebo-controlled study to evaluate the effects of daily oral alpha-lipoic acid supplements (600 mg, three times per day) plus standard medical care in the treatment of painful HIV-associated neuropathy over a 24-week period (60 patients); completed in 2008.			
Glutamine	**clinician-sponsored**	**Phase III**	**energy supply**
NCT00195013: A Randomized Placebo-Controlled Trial of Glutamine to Reduce the Signs and Symptoms of Peripheral Neuropathy in Breast Cancer Patients With a Mild Peripheral Neuropathy Receiving Paclitaxel Chemotherapy (50 patients); under recruitment.			
Vitamin E	**clinician-sponsored**	**Phase III**	**antioxidant**
NCT00363129: The Use of Vitamin E for Prevention of Chemotherapy Induced Peripheral Neuropathy: A Phase III Double-Blind Placebo Controlled Study (200 patients); study ongoing, but not recruiting.			

(*Table continues*)

Table 1. *Continued*

Compounds and Trials	Company	Latest Development Status	Mechanism
Amifostine trihydrate	**clinician-sponsored**	**Phase III; active**	**neuroprotective agent**
NCT00058071: A Randomized Phase III Trial of Amifostine vs. No Treatment for Platinum Induced Peripheral Neuropathy (100 patients); completed in 2008. NCT00078845: Phase II Trial of Subcutaneous Amifostine for Reversal of Persistent Paclitaxel-Induced Peripheral Neuropathy (40 patients); completed. NCT00601198: Phase II Study of the Efficacy of Amifostine (Ethyol) in Reducing the Incidence and Severity of Oxaliplatin-Induced Neuropathy in Patients With Colorectal Cancer (97 patients); active and recruiting; results 2009.			
Acetyl-L-carnitine	**clinician-sponsored**	**Phase III; active**	**neuroprotective agent**
NCT00050271: An Open-Label, Dose-Escalation Pilot Study of Acetyl-L-Carnitine for the Treatment of Dideoxynucleoside-Associated Distal Symmetric Peripheral Neuropathy (36 patients); study ongoing, but not recruiting. NCT00775645: Randomized Placebo-Controlled Trial of Acetyl-L-Carnitine (ALC) for the Prevention of Taxane Induced Neuropathy Phase III. Study in women with stage I, stage II, or stage IIIA breast cancer undergoing chemotherapy (380 patients); not yet recruiting; results 2012. NCT00751205: (REASON) Double-Blind, Randomized Phase II Study to Evaluate the Safety and Efficacy of Acetyl-L-Carnitine in the Prevention of Sagopilone-Induced Peripheral Neuropathy (140 patients); results 2010.			
Olesoxime (TRO19622)	**Trophos**	**Phase II; active**	**neuroprotective agent**
NCT00496457: A Double-Blind, Randomized, Multicenter Study With 500 mg QD of TRO19622 Versus Placebo in Patients With Painful Peripheral Diabetic Neuropathy (180 patients); completed; well tolerated, no improvement compared with placebo. NCT00876538: A Double Blind, Placebo Controlled Study of the Effect of 330 mg QD of TRO19622 in the Treatment of Chemotherapy Induced Peripheral Neuropathy. An exploratory Phase II study of pain, dysesthesia and neuropathy in patients with taxane-induced peripheral neuropathy (40 patients); under recruitment.			

NCT numbers refer to entries at http://www.clinicaltrials.gov.
CIPN = chemotherapy-induced peripheral neuropathy; HIV = human immunodeficiency virus; LV = leucovorin (folinic acid); 5-FU = 5-fluorouracil.

eration of sensory nerve terminals; in this case, neurodegeneration has been shown to reduce pain in animal models and in humans.[68] Various forms of capsaicin are being explored and developed clinically to treat chronic pain syndromes (e.g., NGX-4010, ALGRX-4975). Because TRPV1 receptors are upregulated as well as activated during inflammation, TRPVI antagonists have been hotly pursued as analgesics by pharmaceutical and biotech companies. However, TRPV1 receptors appear to play an important role in central thermal regulation, and the potential for TRPV1 antagonists to induce hyperthermia is an unacceptable adverse effect that is likely to limit their future clinical development.[69]

Increased C-fiber excitability, which has been found in diverse neuropathic pain syndromes, is often correlated with changes in voltage-gated sodium channel expression, distribution, or firing threshold in peripheral sensory neurons.[70–72] Although much attention has been focused on sensory neuron selective sodium channels such as $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ as drug targets to treat pain, their role in neuropathic pain remains controversial. Mutations in $Na_v1.7$ are found in congenital pain syndromes, and knock-down or inhibition of $Na_v1.8$ has been reported to reduce neuropathic pain behavior in animals.[73–76] Surprisingly, neuropathic pain is still present in mice lacking $Na_v1.7$ or $Na_v1.8$ (established using a $Na_v1.8$-driven knock-out strategy) and neuropathic pain behavior is even maintained in mice in which nearly all $Na_v1.8$-positive nociceptors have been ablated.[77–79] Because $Na_v1.8$-expressing nociceptors also express and release BDNF in the spinal cord, perhaps it is the absence of BDNF that changes pain behavior in mice lacking $Na_v1.8$-positive sensory neurons, given the role of BDNF and TrkB in the establishment of some types of persistent pain behavior (although maybe not all types of neuropathic pain—at least not in mice).[62]

Nevertheless, increased expression of sodium channels on nerve terminals and axons would be one mechanism contributing to hyperexcitability and, through increased depolarization, increased intracellular calcium due to activation of voltage-dependent calcium channels. As in multiple sclerosis, in which ectopic expression of sodium channels is believed to contribute to long-term axonal degeneration, long-term overactivation of sensory nerve sodium channels may also contribute to neurodegeneration in neuropathic pain.[80] Although these changes have been documented in diverse animal models, it is not clear whether similar changes in sodium channel expression are present clinically. Nonetheless, local anesthetics, which block voltage-gated sodium channels by binding

to a site within the pore formed by the α-subunit, are used to treat various pain syndromes, including some types of neuropathic pain. If sodium channel hyperexcitability leading to calcium overload is an underlying component of neurodegeneration, local anesthetics might provide neuroprotection; however, the potential for neurologic and cardiac adverse effects limits their usefulness for this purpose.

In axons and nerve terminals, mitochondria play a major role in maintaining ion homeostasis after membrane depolarization by generating ATP to drive plasma membrane Na^+/K^+ ATPase and buffering intracellular calcium. Loss of mitochondrial capacity to provide ATP or to take up calcium could be a factor contributing to the sensory nerve fiber degeneration that occurs in neuropathic pain conditions.

Mitochondrial dysfunction

Oxidative damage resulting from disease or chemical intoxication (chemotherapeutics, alcohol abuse, HAART) occurs in large part because of reactive oxygen species produced by the mitochondrial electron transport chain. Ironically, mitochondria themselves are targets of oxidative damage to their DNA and membranes, both of which lead to mitochondrial dysfunction. The mitochondrial permeability transition pore (mPTP), a protein complex that regulates mitochondrial integrity, is sensitive to thiol oxidation, which facilitates calcium-induced mitochondrial permeability transition.[81]

Proteins that contribute to mPTP and permeability transition include the voltage-dependent anion channel (VDAC), the translocator protein (TSPO; previously known as peripheral benzodiazepine receptor, PBR), the adenine nucleotide translocator (ANT), for which specific thiols have been identified,[82] and cyclophilin D, a prolyl-isomerase that interacts with ANT. Cyclophilin D is the target of Cyclosporin A, a blocker of calcium-induced mitochondrial permeability transition.[83,84] Decreased growth factor signaling through Akt with resulting increased GSK3β activation leads to dissociation of hexokinase from VDAC and increased probability of mitochondrial permeability transition and apoptosis, and it can also increase sensitivity to chemotherapeutic agents.[85]

Microtubule-targeted chemotherapeutic agents also favor mitochondrial permeability pore transition by modulating tubulin-VDAC interaction,[86] and some HAARTs may affect the mPTP by binding to ANT. Swollen and vacuolated mitochondria have been observed clinically and in animal models of diabetes and chemotherapy-induced neuropathic pain.[42,44,87–89] Oxidative stress in diabetic nerve has been suggested to trigger mitochondrial-mediated local apoptosis in nerve terminals leading to axon degradation.[4] However, given that the DRG cell bodies are up to a meter or more away from the nerve terminal, this may not lead to DRG cell death. Loss of nerve terminal–target interaction and mitochondrial supplied energy for retrograde transport and signaling may, however, induce many of the long-term changes in gene and protein expression changes seen after axotomy.

Changes in undamaged nerves induced by neurodegeneration

Although it is obvious that traumatic injury can lead to transient or permanent nerve damage, the behavior of undamaged nerves can be modified by the loss of their neighbors. Changes in gene expression (including upregulation of sodium channels, TRPV1 receptors, BDNF and neuropeptides such as substance P and CGRP) have been found in uninjured DRG neurons after axotomy, either as a result of relatively greater abundance of trophic factors or because of inflammatory responses to damaged tissue.[90–93] Perhaps the combination of damage-induced degeneration and changes in spared neurons distinguishes the neuropathic pain mechanisms after nerve injury from other more systemic causes of neurodegeneration, such as diabetes, chemotherapy, or HAART treatment.

THERAPEUTIC APPROACHES TO TARGETING NEUROPROTECTION

All approved drugs and most of the therapeutic approaches under development aim to reduce symptoms of neuropathic pain, but neuroprotection or even neurorestoration would be even more desirable. Only a few drugs or other agents with direct or indirect neurotrophic activity have been explored or are currently under development for the treatment of peripheral neuropathy (Table 1). Only drugs still under development are detailed here.

Acetyl-L-carnitine: mechanism, efficacy in animal models and the clinic

Acetyl-L-carnitine (ALC), the acetyl ester of L-carnitine, plays an essential role in the metabolism of long chain free fatty acids. Beyond its classical role in energy metabolism, ALC exhibits many others properties, including antioxidant and neuroprotective properties.[94–99] Repeated treatment with ALC also promotes nerve regeneration after nerve axotomy.[100] Reduced levels of ALC were associated with nerve alterations in diabetes and in HIV.[101,102] In diabetic animals, ALC treatment normalizing plasma and nerve L-carnitine levels prevented motor nerve conduction velocity slowing, reduced lipid peroxidation, and restored Na^+/K^+ ATPase activity.[103–107] Both prophylactic and therapeutic treatment with ALC also corrected the thermal hypoalgesia in diabetic mice.[108] In animal models of CIPN, ALC administration promoted the recovery of nerve conduction velocity and significantly prevented or reversed the neuropathic pain syndrome evoked by vincristine, cisplatin, and paclitaxel.[109–112]

Whether mechanisms underlying neuroprotective effects of ALC might be responsible for its analgesic properties is still unclear. *In vitro*, neuroprotective effects of ALC were associated with upregulation of NGF and its receptor.[113–115] In a rat model of chronic constriction injury–induced peripheral neuropathy, treatment with ALC reduced cytochrome *c* release and caspase-3 activation and induced X-linked inhibitor of apoptosis protein (XIAP) expression.[116] Such effects might be mediated through the maintenance of key mitochondrial functions by ALC.[97,117] In paclitaxel-induced painful neuropathy, efficacy of ALC was associated with a reduced incidence of swollen and vacuolated mitochondria in C-fiber.[118] In addition, a more direct effect might explain acute analgesic effects of ALC through upregulation of mGluR2 receptors and downstream activation of endogenous cholinergic activity.[119–122]

In clinical use, ALC is safe and well tolerated.[123] Two large-scale trials have been conducted supporting some clinical efficacy of ALC for the treatment of diabetic peripheral neuropathy.[124] Consistent reduction in pain, however, seems to require long-term treatment (>1 year) and high doses of ALC (>3000 mg daily).[125] Efficacy of ALC was also reported in two pilot trials in patients with paclitaxel or cisplatin-induced neuropathy. In both trials, improvement in the sensory neuropathy grade ranged between 60% to 73% of the patients and persisted after ALC treatment.[126,127] A large randomized placebo-controlled phase III trial is planned to start studying ALC to prevent neuropathy in women with breast cancer undergoing taxane chemotherapy (ClinicalTrials.gov NCT00775645). Similar exploratory studies were conducted in HIV-induced neuropathies and reported some benefit of long-term treatment with ALC.[128,129] Some other studies are still ongoing (ClinicalTrials.gov NCT00225160). Interestingly, Valcour et al. [130] reported no differences in density of intraepidermal nerve fibers or in mtDNA copies per cell after 3000 mg ALC daily for 24 weeks, whereas improvements in neuropathic pain were noted, as previously observed in a preclinical study.[118] Although promising, these results will have to be confirmed in adequately powered placebo-controlled studies to ascertain the potential of ALC to be effective to treat or even prevent painful peripheral neuropathies.

Olesoxime: discovery, mechanism, efficacy in animal models and the clinic

Olesoxime (TRO19622) is a cholesterol-oxime compound originating from the proprietary library of Trophos (Marseille, France). Identified for its survival-promoting properties for motor neurons in culture,[131] olesoxime has been shown to inhibit both intrinsic and extrinsic neuronal death pathways (unpublished data). Beyond neuroprotective properties, olesoxime also promoted nerve regeneration in a number of *in vitro* and *in vivo* models of neurodegeneration. Olesoxime bound directly to two components of the mitochondrial permeability transition pore, VDAC and TSPO. Recent observations also suggest that olesoxime targets tubulin, which has been shown to be in close association with VDAC in mitochondria.[86,132] The current working hypothesis on the mechanism of action of olesoxime is in favor of a tight regulation of mitochondrial pore opening through interactions with these proteins.

Olesoxime significantly reduced axonal degeneration and accelerated recovery of motor nerve conduction in a model of peripheral neuropathy induced by crushing the sciatic nerve, which motivated further exploration in other preclinical models of peripheral neuropathy.[131] Daily oral administration of olesoxime improved motor nerve conduction impaired in streptozotocin-induced diabetic rats and also reversed neuropathic pain behavior as early as the first administration.[133] Olesoxime also reversed tactile allodynia in chemotherapy-induced (vincristine-induced) painful peripheral neuropathy, but had had no analgesic activity per se in formalin- or chronic constriction injury–mediated neuropathic pain models.[133] In paclitaxel-treated rats, olesoxime also reversed mechano-allodynia and mechano-hyperalgesia in both preventive and prophylactic treatment paradigms and significantly reduced the amount of paclitaxel-induced sensory terminal arbor degeneration (unpublished data). Mitochondrial dysfunction was proposed to be a common mechanism for both painful diabetic and chemotherapy-induced neuropathies, which supports the presumed olesoxime mechanism of action.[4,42,89] However, how modulation of mitochondrial function may explain the acute effects of olesoxime on neuropathic pain remains to be determined.

Orally administered, olesoxime is well tolerated and has an excellent clinical safety profile in humans. Its efficacy was evaluated in a multicenter, randomized, double-blind, placebo-controlled phase IIa clinical trial including 187 patients with painful peripheral diabetic neuropathy. Although olesoxime treatment (500 mg daily, p.o., for 6 weeks) was very well tolerated in this patient population, the primary endpoint of the trial, a significant decrease in mean pain score as measured on the Likert scale, was not met. These disappointing results raise the question of the predictability of preclinical acute models for diabetic peripheral neuropathy induced by streptozotocin, which may not reflect the pain syndrome associated with chronic diabetes in humans.[134] Based on preclinical results in both vinca alkaloid- and taxane-induced painful neuropathies, an exploratory phase IIa study was launched in patients with paclitaxel-induced neuropathy to test reversion of pain syndromes and improvement in nerve conduction after olesoxime treatment. Efficacy results are expected in 2010.

Nonpeptide neurotrophic factor modulators

Many drugs shown to stimulate endogenous neurotrophic factor expression have been developed and tested in peripheral neuropathies (Table 1). Among these, xaliproden (SR 57746A; 1-[2-(naphth-2-yl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,5,6-tetrahydropyridine HCl), which is a synthetic 5-HT_{1A} receptor agonist and an inducer of NGF synthesis, possesses neurotrophic activity in a variety of neurodegenerative models *in vivo*, including peripheral neuropathies.[135–137] Notably, xaliproden was reported to lessen oxaliplatin-mediated neuropathy in a large, randomized, double-blind, placebo-controlled phase III study ($n = 649$).[138,139] Although the use of xaliproden in this trial was not associated with a higher cumulative oxaliplatin dose or with a longer time on therapy, patients in the xaliproden arm had a significant (39%) risk reduction of developing grade 3/4 neuropathy. A phase III trial in approximately 900 patients is ongoing to confirm these results (NCT00305188), as well as a trial in ~250 subjects to assess the effect of xaliproden to treat the peripheral sensory neuropathy resulting from oxaliplatin-based chemotherapy (NCT00603577).

MCC-257, an orally active sialic acid derivative, augmented NGF activity in cultured dorsal root ganglia and has neuroprotective properties in diabetic peripheral nerves.[140] Its safety and efficacy was evaluated in a phase II, randomized, double-blind, placebo-controlled trial in 420 patients with mild to moderate diabetic polyneuropathy (NCT00307749). Results were not disclosed.

Leteprinim (Neotrofin, AIT-082; further developed as SPI-205) induces expression of several neurotrophic factors in various areas of the brain and spinal cord and prevented depletion of NGF in plantar foot skin and sciatic nerve of diabetic rats.[141] SPI-205 is under clinical development for treatment of chemotherapy-induced neuropathy (http://www.spectrumpharm.com).

TAK-428 enhances neurotrophic factor production and is under development by Takeda Pharmaceutical (Osaka, Japan) for the treatment of diabetic neuropathy. It is currently in phase II in the European Union and in the United States.

TSPO ligands (SSR180575)

The peripheral benzodiazepine receptor (PBR), recently renamed translocator protein 18 kDa (or TSPO, as noted earlier in this review), is an outer mitochondrial membrane protein implicated in mitochondrial cholesterol uptake and steroidogenesis; it is a well known target for neuroprotection.[142–144] SSR180575 (7-chloro-*N*,*N*,5-trimethyl-4-oxo-3-phenyl-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indole-1-acetamide) is a novel specific and potent TSPO ligand improving functional recovery in rat models of peripheral neuropathy.[145,146] SSR180575 increased pregnenolone accumulation in the brain and sciatic nerve (100% increase at 3 mg/kg, i.p.), suggesting that its neuroprotective effects are steroid-mediated. SSR180575 is under current clinical investigation in patients with mild diabetic peripheral neuropathy (NCT00502515).

CONCLUSIONS

Neuropathic pain, as the term implies, is due to an intrinsic pathology of the nerve. This distinguishes it from acute or inflammatory pain arising from outside the nerve, through release of neuromediators or cytokines from neighboring cells that directly and transiently activate a range of receptors and ligand-gated ion channels. Preventing neuropathic pain in cases in which it is most prevalent seems, at least on the face of it, a feasible goal. Nonetheless, much more needs to be known about the mechanisms of neurodegeneration in each condition to know what neuroprotective strategy is likely to be most effective. Although studying a treatment to assess its ability to reverse a condition is not a regulatory or technical challenge, identifying targets or critical processes with the intention of reversing neuropathic pain is an enormous conceptual challenge that has so far effectively stymied drug discovery.

In the case of diabetes, the disease process leading to neuropathy and pain is slow and probably involves not only axonal damage that may misalign sensory signaling but also causes, over time, long-term changes in central processing of sensory information, including seemingly irreversible changes in gene expression. These changes occur gradually, and may not be perceptible before the damage or central plasticity has gone too far to be reversed. If neuropathic pain is similar to other types of neurodegeneration, oxidative stress combined with calcium overload triggered by various factors may be a common underlying mechanism. Although antioxidants such as α-lipoic acid, ALC, and Vitamins E and C have been studied in a large number of neurodegenerative conditions, including painful neuropathies, with some promising results (Table 1), none have yet to be approved to treat these indications. Thus, either an antioxidant alone is not able to provide sufficient benefit or the treatment does not reach the appropriate target at high enough concentration or for long enough a time to provide relief.

Antioxidants are believed to improve mitochondrial function by reducing mitochondrial membrane or DNA damage. Other drugs targeting mitochondria in clinical development are TSPO ligands that reduce apoptosis correlated with increased mitochondrial cholesterol uptake and steroidogenesis. A trial of SSR180575 in 270 diabetic patients to determine whether this drug can enhance regeneration after capsaicin-induced nerve terminal lesion has recently been completed. This exploratory

study might have been the prelude for a larger and longer clinical trial of its ability to reverse established diabetic neuropathy; however, this compound has recently been dropped from the clinical development pipeline, so one can speculate that either the clinical results were not compelling or the development plan was considered too long, complicated, and costly.

Although mitochondrial protection seems attractive as a general mechanism, it may not be the only strategy and may not be sufficiently effective on its own or in all conditions. For example, olesoxime did not improve pain compared with placebo in patients with painful diabetic neuropathy, although no measurement of the effect on neuropathy was made in this short, 6-week trial (Table 1). A study of olesoxime in a small number of patients with paclitaxel-induced neuropathic exploring both pain and neuropathy endpoints began recruiting patients early in 2009. Besides mitochondrial protection, other downstream mediators of stress signaling arising from mitochondrial dysfunction, such as p38 kinase, may also be useful targets, either alone or in combination with other approaches.

Testing a promising neuroprotective drug in patients with a chronic disease such as diabetes prior to the onset of neuropathic pain is, unfortunately, not practical because of the long time course (decades) and variable incidence of painful neuropathy, which, though common, occurs in only some 30% of patients; a study involving several hundred patients over a decade would be necessary to demonstrate efficacy without some way of identifying which patients would be most at risk of developing neuropathic pain. Thus, the first trials of neuroprotective agents to treat chronic painful neuropathies are likely to be in conditions in which the cause and effect are more closely linked in time, such as PHN and chemotherapy-induced neuropathic pain. Because gabapentin and its analog pregabalin, along with topical lidocaine and most recently NGX-4010 are all approved for the treatment of PHN, treatments targeting neuroprotection will be confounded by the need to perform trials in patients treated with these agents that either block or ablate nerve conduction or transmission.

Chemotherapy-induced painful neuropathy may be the simplest indication in which to test a neuroprotective therapeutic. It is the direct consequence of the chemotherapeutic regime, the time course of onset is shorter (compared with diabetes) and more predictable, in that it is related to the cumulative dose; however, it develops only in a subset of patients depending on the type of chemotherapeutic agent (as discussed above). Therefore, clinical trials to test whether neuroprotection might prevent the onset of painful neuropathy could seem at first glance quite feasible. Nonetheless, because the incidence of severe pain is variable, a large number of patients are likely to be required if the beneficial effects are modest or occur in only a subpopulation. For example, the two studies with xaliproden to prevent oxaliplatin-induced neuropathies recruited 650 and 900 patients, respectively (Table 1). In the case of chemotherapy-induced neuropathy, the initial recruitment has to take into account the loss of patients over the course of the trial (cancer-related deaths and discontinuation of treatment because of neuropathy) to be sure that at the end of the trial the number of subjects who have completed the trial provide sufficient power to conclude efficacy.

Another consideration to take into account is whether the mechanism of action of a neuroprotective drug may adversely affect the efficacy of the chemotherapy. Preclinical studies in tumor xenograft models are required before initiating clinical trials, in which responder rates can be used to assure no negative consequence of the neuroprotective agent. Finally, when a neuroprotective treatment is available for testing, enrollment criteria for the clinical trial may be very narrow, such that few patients qualify: for example, the type of chemotherapy used, whether the patient has received previous types of chemotherapy, and potential to complete the trial (i.e., life expectancy). Such restrictions can make the time to recruit the defined patients longer than a company or funding agency can support.

Testing whether neuroprotection may reverse or accelerate recovery from chemotherapy-induced painful neuropathy is also straightforward: it is necessary only to identify subjects who have completed their course of chemotherapy and have developed neuropathic pain. Although this sounds simple, execution is complicated: enrollment criteria must be tightly defined, making few patients eligible, and the cancer must be sufficiently controlled to allow patients to stop chemotherapy during the course of the trial for as long as 6 months or more (first the time to complete the pre-trial screening process and then treatment for at least 3 months). Nevertheless, both prevention and treatment of chemotherapy-induced painful neuropathy are of medical concern, because this condition is a major reason for patients to stop chemotherapy. By allowing patients to continue their cancer treatment longer, an effective neuroprotective drug could increase both survival and quality of life.

Although reversing or preventing the neurodegenerative processes that underlie neuropathic pain by targeting neuroprotection is a path worth exploring, the challenges are enormous. For companies, the ultimate objective is a treatment that will be effective in the maximum number of subjects. Unfortunately, the various pain syndromes collectively labeled *neuropathic pain* have diverse underlying causes, including trauma, viral infection, inflammation, metabolic disturbances, and therapeutic or other chemical intoxication. Each represents only a niche market, and targeting therapies to one indication does not mean they will treat another. Chemotherapy-induced

painful neuropathies are refractory to current drugs approved for painful diabetic neuropathy or PHN.

A noteworthy central mediator of various types of nontraumatic stress-induced painful neuropathies appears to be mitochondrial dysfunction, due to and then contributing to oxidative damage and calcium overload. Given that targeting mitochondrial dysfunction is a strategy to treat other neurodegenerative diseases, such as Alzheimer's disease, the massive research and development efforts dedicated to this indication will, we can hope, lead to a breakthrough allowing targeting neuroprotection for neuropathic pain syndromes.[147]

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