L-Acetylcarnitine: A Proposed Therapeutic Agent for Painful Peripheral Neuropathies

S. Chiechio[1], A. Copani[2], F. Nicoletti[3], and R. W. Gereau IV[1,*]

[1]*Washington University Pain Center and Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO, USA;* [2]*Department of Pharmaceutical Sciences, University of Catania, Catania, Italy;* [3]*Department of Human Physiology and Pharmacology, University of Rome 'La Sapienza', Faculty of Medicine, Rome, Italy and Istituto Neurologico Mediterraneo, Neuromed Pozzilli (IS), Pozzilli, Italy*

Abstract: During the past two decades, many pharmacological strategies have been investigated for the management of painful neuropathies. However, neuropathic pain still remains a clinical challenge. A combination of therapies is often required, but unfortunately in most cases adequate pain relief is not achieved. Recently, attention has been focused on the physiological and pharmacological effects of L-acetylcarnitine in neurological disorders. There are a number of reports indicating that L-acetylcarnitine can be considered as a therapeutic agent in neuropathic disorders including painful peripheral neuropathies. In this review article, we will examine the antinociceptive and the neuroprotective effects of L-acetylcarnitine as tested in clinical studies and in animal models of nerve injury.

Key Words: L-acetylcarnitine, neuropathic pain, peripheral neuropathies, antinociception.

INTRODUCTION

SYMPTOMATOLOGY AND PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

Neuropathic pain is a severe and debilitating condition which affects approximately 6 million people in the U.S. alone [2]. It accounts for a large number of patients presenting with chronic pain of nonmalignant origin. Neuropathic pain is the expression of pathological changes in the peripheral and central nervous system and may result from nerve damage caused by a variety of insults including traumatic nerve injury, metabolic diseases, viral infections, or stroke.

A combination of positive and negative sensory symptoms often occurs in neuropathic pain patients. These can be summarized as follows: paresthesias (numbness or tingling), dysesthesias (electric shock phenomenon), hyperesthesia (increased sensitivity to mild painful stimuli), hyperalgesia (increased sensitivity to normally painful stimuli), hyperpathia (pain produced by subthreshold stimuli) spontaneous pain and allodynia (pain produced by normally non-painful stimuli) [55].

Both peripheral and central mechanisms are involved in the development and maintenance of neuropathic pain. Damage to peripheral nerves is usually the first step that triggers the cascade of biochemical events and adaptive mechanisms leading to peripheral and central sensitization processes. During prolonged pain states, adaptive modifications of receptors and ion channels as well as changes in gene expression occur in sensory neurons in dorsal root ganglia (DRG) and in the dorsal horn (DH) of the spinal cord [56]. Also, alteration of local or descending inhibitory systems contributes to a hyperexcitability that predominates in chronic pain states. At the cellular level, one mechanism by which pain sensitization can be produced is the increased expression of sodium channels along the nerve and in the cell bodies of neurons in the DRG. This can lead to increased excitability and generation of ectopic discharges [53]. Under these conditions, enhanced activity of primary afferents results in the release of excitatory amino acids and peptides, such as substance P, in the DH, and this increased transmitter release leads to the establishment of central sensitization [11].

These mechanisms, together with the abnormal reorganization of neuronal circuits in the DH and the spontaneous activity of primary afferents, contribute to the genesis of the phenomenon of spontaneous pain, increased sensitivity to noxious stimuli and allodynia in neuropathic pain states. Moreover, the intense neurotransmitter release from primary afferent neurons in the DH is also responsible for the activation of microglia and subsequent release of chemokines and pro-inflammatory cytokines which have been demonstrated to mediate not only the increased pain sensitivity in inflammatory pain but also the abnormal pain sensitivity in neuropathic states [34].

ETIOLOGY OF THE MAJOR FORMS OF NEUROPATHIC PAIN

There are many forms of neuropathic pain that can be generated from different types of injury to the nervous system (Table **1**). Painful diabetic neuropathies, distal symmetrical polyneuropathies associated with HIV infection and postherpetic neuralgia are among the most common causes of neuropathic pain encountered in clinical practice. However, nerve damage can also be a result of drug toxicity or central dysfunctions that include central poststroke pain, HIV myelopathy, multiple sclerosis pain, Parkinson's disease pain, spinal cord injury pain and syringomyelia [5,30,31,45,51,56].

*Address correspondence to this author at Department of Anesthesiology, Washington University School of Medicine, 660 S. Euclid Ave, Campus Box 8054, St Louis, MO 63110, USA; E-mail: gereaur@wustl.edu

Table 1.   Common Etiologies of Neuropathic Pain

Peripheral neuropathies
- Diabetic neuropathy
- HIV-associated sensory neuropathy
- Postherpetic neuralgia
- Traumatic peripheral neuropathies
- Entrapment neuropathies
Central Neuropathies
- Poststroke pain
- Multiple Sclerosis
- Parkinson's disease
- HIV myelopathy
- Spinal cord injury
- Syringomyelia
Cancer-associated neuropathies
- Nerve compression caused by tumor growth
- Asymmetric neuropathies caused by nerve infiltration
Idiopathic neuropathies
- Chemotherapeutic agents
- Antiretroviral nucleoside analogs

Despite the numerous pharmacological agents available for the treatment of painful neuropathies, the management of this kind of pain remains extremely difficult. Neuropathic pain is very often refractory to the standard analgesics used in pain therapy and, additionally, patients with a similar pathology may respond with a large degree of variability to the same pharmacological treatment. The current pharmacological approaches to the treatment of neuropathic pain include the use of several agents alone or in combination. Among these, opioids, anticonvulsants, antidepressants, local anesthetics, selective sodium channel blockers, alpha-2 agonists, and topical agents, are the most prescribed drugs [12,18,42,50,55,]. However due to the chronic nature of neuropathic pain, drugs that are effective in a first stage of the pathology may become ineffective because of the development of mechanisms of tolerance or may not be very well tolerated after chronic administration.

Clearly, the development of novel forms of treatment for neuropathic pain conditions is needed. This effort should include not only mechanism-based bottom-up approaches that are being aggressively pursued by pharmaceutical companies, but also the detailed examination of agents currently in use for which efficacy and mechanisms of action have not been clearly determined. In this review, we will discuss one such agent: L-acetylcarnitine. There are anecdotal reports and some information from limited clinical trials suggesting that this agent may be efficacious in the management of cer-

tain forms of neuropathic pain. In addition, animal studies suggest some potential underlying mechanisms. In this review, we discuss the effects of L-acetylcarnitine in different forms of pain in animal models and in clinical studies of human peripheral neuropathies.

BIOLOGICAL PROPERTIES OF L-ACETYLCARNITINE

L-Acetylcarnitine is the acetyl ester of L-carnitine, a fundamental compound that plays an essential role in the metabolism of fatty acids in mitochondria [3]. In mammalian tissues, L-acetylcarnitine is synthesized from the amino acid carnitine by the enzyme carnitine acetyltransferase (CRAT) [6] for which the crystal structure has been recently reported [27]. Both L-acetylcarnitine and CRAT are widely distributed in mammalian tissues, including the brain [46]. Exogenously administered L-acetylcarnitine is transported into the brain through an active transport mediated by a high affinity organic cation/carnitine transporter (OCTN2) that is functionally expressed in the blood-brain barrier of mammals [25,29]. Aside from its role in fatty acid β-oxidation, many other functions have been attributed to L-acetylcarnitine. It has been reported that L-acetylcarnitine modulates the activity of nerve growth factor (NGF) in the nervous system in rats [1,40,52], increases the activity of choline acetyltransferase, enhances the expression of NGF receptors in the striatum and hippocampus of rats during development [10] and modulates different neurotransmitter systems including the cholinergic and dopaminergic system [24,20]. Additionally L-acetylcarnitine functions as a donor of acetyl groups in oxidative glycolysis [4] and can also have important biological function due to its ability to contribute to acetylation of -OH or $-NH_2$ functional groups on amino acids and N-terminal groups in proteins and peptides [39].

EFFECTS OF L-ACETYLCARNITINE IN EXPERIMENTAL MODELS OF ACUTE AND NEUROPATHIC PAIN

The antinociceptive effect of L-acetylcarnitine has been shown in different pain models in rodents [7,14,15], and several mechanisms have been proposed. Indirect activation of muscarinic receptors as well as the activation of the PLC-IP_3 pathway has been postulated to mediate the antinociceptive effect of L-acetylcarnitine in experimental models of acute pain [14,15]. Moreover, increased expression of metabotropic glutamate receptor 2 (mGlu2) in regions of the nervous system involved in pain transmission after chronic administration of L-acetylcarnitine has been proposed to account for the antinociceptive efficacy of the drug in acute pain and in chronic pain after nerve injury in rats [7]. *In vitro* studies performed in cultured DRG neurons showed that the increased expression of mGlu2 receptors occurs mainly in the large diameter neurons from which large myelinated A-beta fibers originate [8]. The finding that the mGlu2/3 agonist, LY379268, is able to induce a marked decrease of NMDA-evoked glutamate release in L-acetylcarnitine treated DRG cultures [8] provides a potential mechanism for the antiallodynic effect of L-acetylcarnitine observed in neuropathic rats [7].

Chronic administration of L-acetylcarnitine has also been studied in experimental models of axotomy and diabetic neuropathy. L-acetylcarnitine prevents the reduced nerve conduction velocity observed in streptozotocin-induced diabetes in rats [32,33,41,48,38] and promotes nerve regeneration [48]. L-acetylcarnitine-induced improvement of nerve regeneration together with prevention of neuronal sensory loss has also been observed in rats following peripheral nerve axotomy [21,22,54]. The neuroprotective effect of L-acetylcarnitine has also been observed in primary neuronal cultures from rat cerebral cortex, striatum, and thalamus, where L-acetylcarnitine was shown to prevent apoptotic cell death induced by serum deprivation [26]. Experiments in cultured DRG neurons from diabetic rats have also shown improvement in retrograde axonal transport after L-acetylcarnitine treatment [28].

Recent studies from Ghirardi and colleagues showed that L-acetylcarnitine treatment is able to reverse mechanical allodynia in several paradigms of anticancer drug-induced neuropathic pain. In this study, a strong mechanical allodynia was induced by the administration of different anticancer drugs such as paclitaxel, cisplatin and vincristine. Interestingly L-acetylcarnitine treatment was able to prevent the development of mechanical allodynia not only when the treatment started together with the anticancer drug but also when the treatment was started after mechanical allodynia had developed [16,17].

EFFECTS OF L-ACETYLCARNITINE IN CLINICAL PAINFUL NEUROPATHIES

Over the last decade, several clinical studies have been designed to evaluate the analgesic effect of L-acetylcarnitine against different types of painful neuropathies. Promising results come from clinical trials for diabetic and HIV-related neuropathies.

Diabetic Neuropathy

An estimated 25% of patients suffering from diabetes mellitus are affected by peripheral neuropathy [44]. Symptoms may involve the sensory and motor systems. A common form of diabetic neuropathy is distal symmetric sensorimotor polyneuropathy (DPN), which is characterized by the development of segmental demyelination. Numbness, tingling, pain, vibratory hypoesthesia to the low extremities, and motor deficits are some of the clinical signs of DPN.

The potential therapeutic efficacy of L-acetylcarnitine treatment of diabetic neuropathy has been evaluated in large randomized placebo-controlled trials [9,47]. After 1 year of treatment with L-acetylcarnitine, improvements were observed in both electrophysiological parameters and pain. In the study conducted by De Grandis and Minardi, sensory nerve conduction velocity (SNCV) in large myelinated fibers of the sural and ulnar nerves and motor nerve conduction velocity (MNCV) were used as parameters for assessing the degree of neuropathy. L-acetylcarnitine treatment significantly improved SNCV and pain sensation relative to placebo [9].

A significant improvement of vibration perception threshold and in pain scores after 1 year of L-acetylcarnitine treatment was observed by Sima and colleagues [47], who evaluated databases from two randomized placebo control trials testing two doses of L-acetylcarnitine (500 and 1000 mg/day, t.i.d.). Interestingly, improvement in paresthesia and hyperesthesia was associated with a significant increase of myelinated fiber numbers, clusters of regenerating fibers, and fiber size in sural nerve biopsies of patients treated with L-acetylcarnitine. In contrast to the study conducted by De Grandis and Minardi [9], no differences in NCV were observed. However, it must be noted that different doses of L-acetylcarnitine and treatment modality were used in the two trials. In both studies patients who showed the greatest response to L-acetylcarnitine were those with type 2 diabetes of short duration. L-Acetylcarnitine was well tolerated and there was no difference in the incidence of adverse effects between patients treated with placebo and those treated with L-acetylcarnitine [9,47].

HIV-Associated Sensory Neuropathy

More than the 34% of patients with HIV develop peripheral neuropathies [19]. Open studies involving HIV-positive patients have shown that a chronic treatment with L-acetylcarnitine improved pain symptoms related to peripheral polyneuropathy [23,43]. Recently, Hart and colleagues reported that six months of oral L-acetylcarnitine treatment resulted in peripheral nerve regeneration of small sensory fibers as observed from skin biopsies in patients with distal symmetrical polyneuropathy [23].

Severe neuropathy is also a potential consequence of antiretroviral therapy used for HIV treatment. After treatment with antiretroviral drugs, 10-30% of patients report signs of drug-associated peripheral neuropathies, such as a bilateral pain and burning dysesthesia in the lower extremities [49,37,35,36]. In a non-randomized clinical trial, Famularo and colleagues reported that HIV patients with lower levels of L-acetylcarnitine in their sera developed painful peripheral neuropathies during treatment with synthetic nucleoside analogues such as Zidovudine (ZDV) or Didanosine (ddI), whereas patients that did not experience peripheral neuropathies during ZDV or ddI treatment had normal levels of L-acetylcarnitine [13]. The effect of chronic administration of L-acetylcarnitine has been evaluated in patients with distal symmetric neuropathy caused by antiretroviral therapy. Hart and colleagues reported that after 6 month oral administration, L-acetylcarnitine induced regeneration of small sensory fibers as observed from immunostaining quantification in skin biopsies of HIV patients with established antiretroviral toxic neuropathy. Cutaneous reinnervation was significantly increased after 6 months of treatment and a further improvement was also observed after a 24-month period of L-acetylcarnitine treatment [23].

CONCLUSION

Despite the different etiologies leading to neuropathic pain, increased neuronal excitability is thought to be the underlying mechanism of all forms of painful neuropathies. Therefore, the current pharmacotherapy of neuropathic pain generally involves the use of drugs that either reduce neuronal discharge or increase endogenous antinociceptive systems. Sodium-channel blockers, antiepileptic agents, opiods,

tricyclic antidepressants, gabapentin etc., have been employed to treat the painful symptoms of different forms of neuropathies. However, although the main goal is to reduce pain and minimize side effects of drugs, the management of neuropathic pain should also be addressed to counteract the pathological changes that occur in many forms of neuropathies. Loss of small sensory fibers, demyelination and changes in nerve conduction velocity are common features in different forms of neuropathies. In this respect, L-acetylcarnitine is a promising compound for the treatment of painful neuropathies for its dual mechanisms, which include a significant analgesic effect after chronic administration and the ability to promote peripheral nerve regeneration and to improve vibration perception. Moreover, the apparent lack of side effects suggests that this drug might be suitable for long term treatment, an important characteristic for a chronic condition such as neuropathic pain. Thus, the data to date suggest that L-acetylcarnitine could be considered for use in neuropathic pain conditions alone or in combination with other treatments. Further large-scale controlled clinical trials are needed to assess the efficacy of L-acetylcarnitine in various neuropathic pain conditions.

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