

L-acetilcarnitina

**NEUROPATIE
PERIFERICHE DI DIVERSA
EZILOGIA**

L-Acetylcarnitine in the Treatment of Patients with Peripheral Neuropathies

A Short Term, Double-Blind Clinical Study of 426 Patients

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Summary

426 patients with peripheral motor or sensory neuropathies were recruited and randomly assigned to 2 treatment groups in a double-blind, 30-day, prospective trial comparing L-acetylcarnitine (LAC) [1000 mg/day intramuscularly for the first 10 days then 2000 mg/day orally for the remaining 20 days] with placebo. Treatment efficacy was assessed by commonly employed electrophysiological tests performed at baseline and at the end of treatment. Safety and tolerability evaluations were performed on the entire patient population, although the statistical analysis for efficacy was restricted to the 298 patients with lower-than-normal nerve conduction velocities (CVs) at baseline. Among patients with impaired motor nerve function, a statistically significant improvement in mean CV ($p < 0.01$ vs placebo) was detected in LAC-treated individuals with mononeuropathies, whereas no statistical difference emerged between the LAC- and placebo-treated groups in patients with motor nerve polyneuropathies. In contrast, there were statistically significant differences between the LAC and placebo groups in terms of improvement in mean CV in patients with sensory nerve mononeuropathies ($p < 0.05$) and in those with sensory nerve poly-

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"L-ACETYLCARNITINE IN THE TREATMENT OF PATIENTS WITH PERIPHERAL NEUROPATHIES"

A Short-Term, Double-Blind Clinical Study of 426 Patients

- **STUDIO CLINICO A BREVE TERMINE
IN DOPPIO CIECO RANDOMIZZATO
VERSO PLACEBO**
- **426 PAZIENTI CON NEUROPATIE
PERIFERICHE AD EZIOLOGIA VARIA**

L-ACETYLCARNITINE

IN THE TREATMENT OF PATIENTS WITH PERIPHERAL NEUROPATHIES

NUMERO DI PAZIENTI SECONDO GRUPPO DI TRATTAMENTO

Patients	LAC	Placebo	Total
Enrolled	210	216	426
Completed	189	205	394
Withdrawald	21	11	32

Abbreviation: LAC = L-acetylcarnitine

PAZIENTI SECONDO GRUPPO DI DIAGNOSI

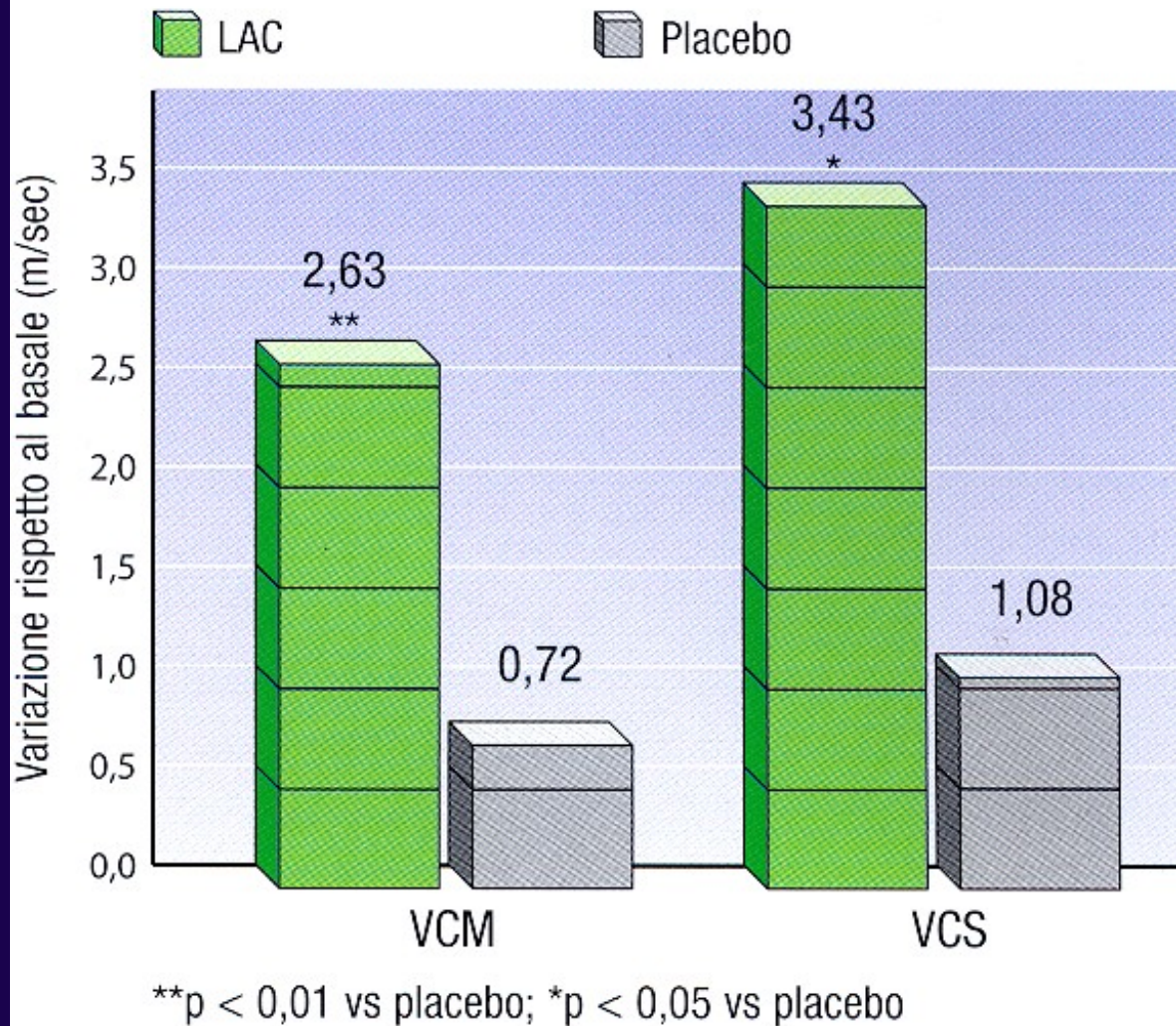
Type of neuropathy	N° of patients	%
Diabetic	56	13.1
Alcoholic	60	14.1
Idiopathic	100	23.5
Traumatic	73	17.1
Compressive	60	14.8
Carpal tunnel syndrom	32	7.2
Infective	10	2.3
Toxic	11	2.6
Guillain-Barré	8	1,6
Vascular	7	1.6
Deficiency	4	0.9
Others ^a	5	1.2
Total	426	100

a Paraneoplastic Neuropathy facial nerve idiopathic paralysis

RISULTATI

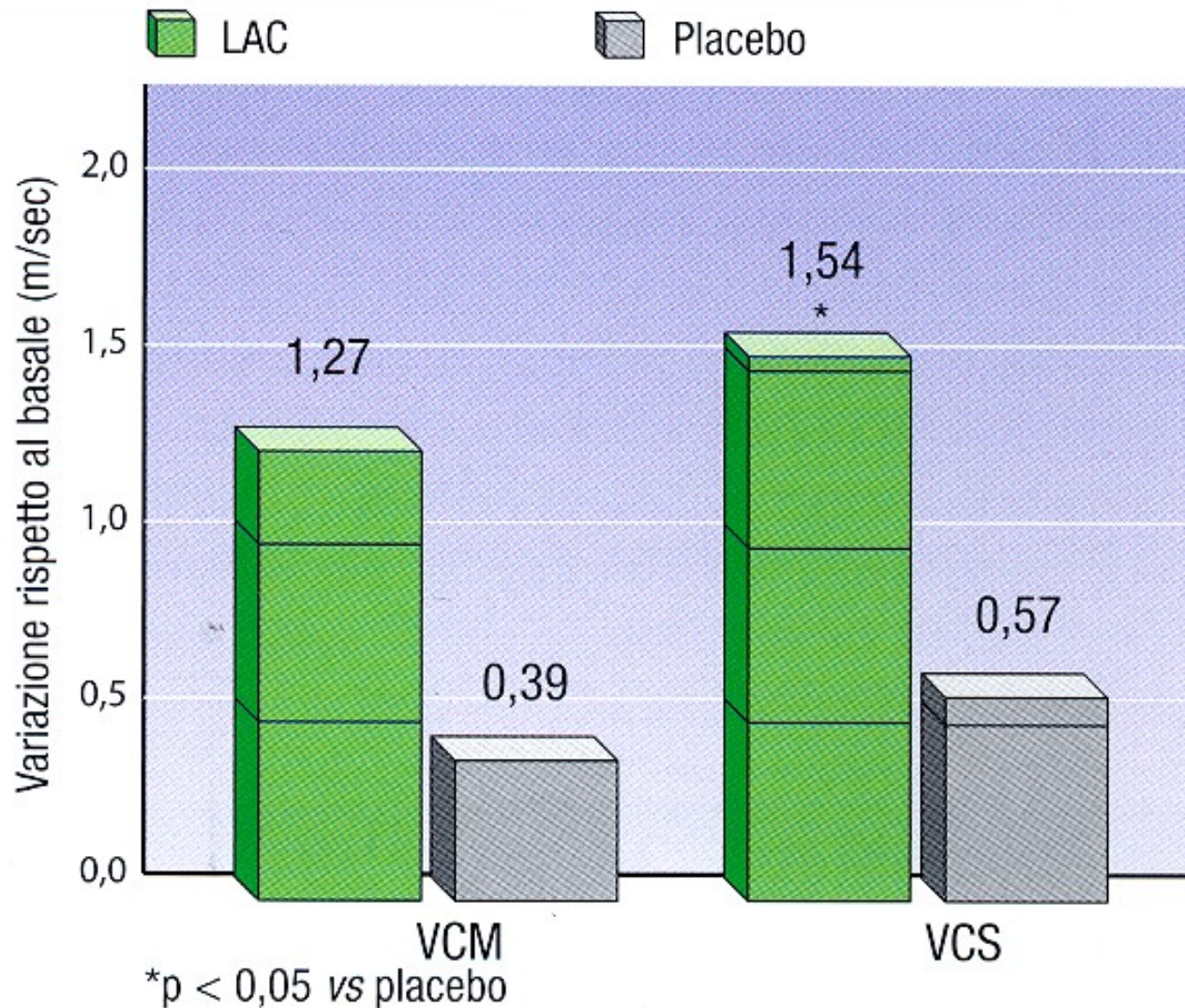
De Grandis D. et al., *Clin Drug Invest*; 1995

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1995



Variazione media della velocità di conduzione nervosa (VCM) e sensitiva (VCS) dopo trattamento per 30 giorni con LAC o placebo nei pazienti con *mononeuropatie*. Nei pazienti affetti da *mononeuropatie*, LAC ha migliorato significativamente sia la VCM sia la VCS.

De Grandis D. et al.,
Clin Drug Invest;
1995



Variazione media della velocità di conduzione nervosa (VCM) e sensitiva (VCS) dopo trattamento per 30 giorni con LAC o placebo nei pazienti con *polineuropatie*. Nei pazienti affetti da *polineuropatie*, LAC ha migliorato significativamente la VCS ($p > 0,05$).

L-acetilcarnitina

AZIONE NEUROTROFICA

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LAC aumenta i livelli del *Nerve Growth Factor* (NGF) e ne potenzia l'attività; inoltre LAC evita la perdita dei recettori per l'NGF.

Queste azioni favoriscono la rigenerazione delle fibre nervose

TAGLIALATELA G. et al.

EXP GERONTOL, 1994, VOL/ISS/PG. 29/1 (55-66)

L-acetilcarnitina

**MECCANISMO
DELL'AZIONE ANTALGICA**

L-Acetylcarnitine Induces Analgesia by Selectively Up-Regulating mGlu2 Metabotropic Glutamate Receptors

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ABSTRACT

L-Acetylcarnitine (LAC, 100 mg/kg, s.c.), a drug commonly used for the treatment of painful neuropathies, substantially reduced mechanical allodynia in rats subjected to monolateral chronic constriction injury (CCI) of the sciatic nerve and also attenuated acute thermal pain. To test this, in both cases, evaluation of

Reverse transcription-polymerase chain reaction combined with Northern blot analysis showed that repeated LAC injections selectively induced mGlu2 mRNA in the dorsal horns and cerebral cortex (but not in the hippocampus). mGlu2 mRNA levels did not change in any brain region of LAC-treated animals. To examine if mGlu2 receptors had any effect on pain, we examined the effect of the novel compound on acute pain in intact rats. LAC (100 mg/kg, s.c.) was largely reduced acute pain in intact rats. This effect was not observed in rats with CCI. LAC produces analgesia by peripheral nerve injury and that LAC-induced analgesia is associated with selective up-regulation of mGlu2 receptors in the dorsal horns and cerebral cortex. This offers the first evidence that LAC-induced analgesia is associated with selective up-regulation of mGlu2 receptors and discloses a novel mechanism for drug-induced analgesia.

Neuropathic pain is characterized by spontaneous pain, allodynia, hyperalgesia, and pain that is exacerbated by non-painful stimuli. In animal models of neuropathic pain, a sustained release of glutamate and peptides induce long-term potentiation at the synapse between primary afferent fibers and second-order neurons in the dorsal horn (Dworkin et al., 1990). Induction of long-term potentiation is associated with an increase in the number of AMPA receptors and changes in their subunit composition (Muller and Malenka, 1992; Malenka et al., 1993; Mott and Malenka, 1993). Particular attention has been given to the role of metabotropic glutamate receptors (mGluRs) that mediate excitatory synaptic transmission and are there-

fore potential targets for "anti" drugs of neuropathic pain. mGluRs are subdivided into eight groups (named mGlu1 to mGlu8) on the basis of sequence homology, pharmacology, and transduction pathways. Group I mGlu receptors (mGlu1 and -5) are coupled to phospholipase C hydrolysis, whereas members of group II (mGlu2 and -3) and group III (mGlu4, -6, -7, and -8) receptors are coupled to G proteins in heterologous expression systems (reviewed by De Biasi et al., 2001). In the dorsal horns, mGlu1 and mGlu5 are found in laminae I and II, whereas mGlu2/3 are found in the inner part of lamina II (Jia et al., 1996; Berthale et al., 1997; Berthale et al., 1999; Tao et al., 2000). mGlu4 and -7 receptors are found in the superficial laminae of the dorsal horns (Li et al., 2001). The use of neutralizing and novel subtype-

Keywords: neuropathic pain; L-acetylcarnitine; mGlu2; chronic constriction injury; analgesia; RT-PCR; reverse transcription-polymerase chain reaction

UP-REGULATION SELETTIVA DEI RECETTORI METABOTROPICI PER IL GLUTAMMATO mGlu2: UN NUOVO MECCANISMO PER SPIEGARE L'ANALGESIA DA L-ACETILCARNITINA

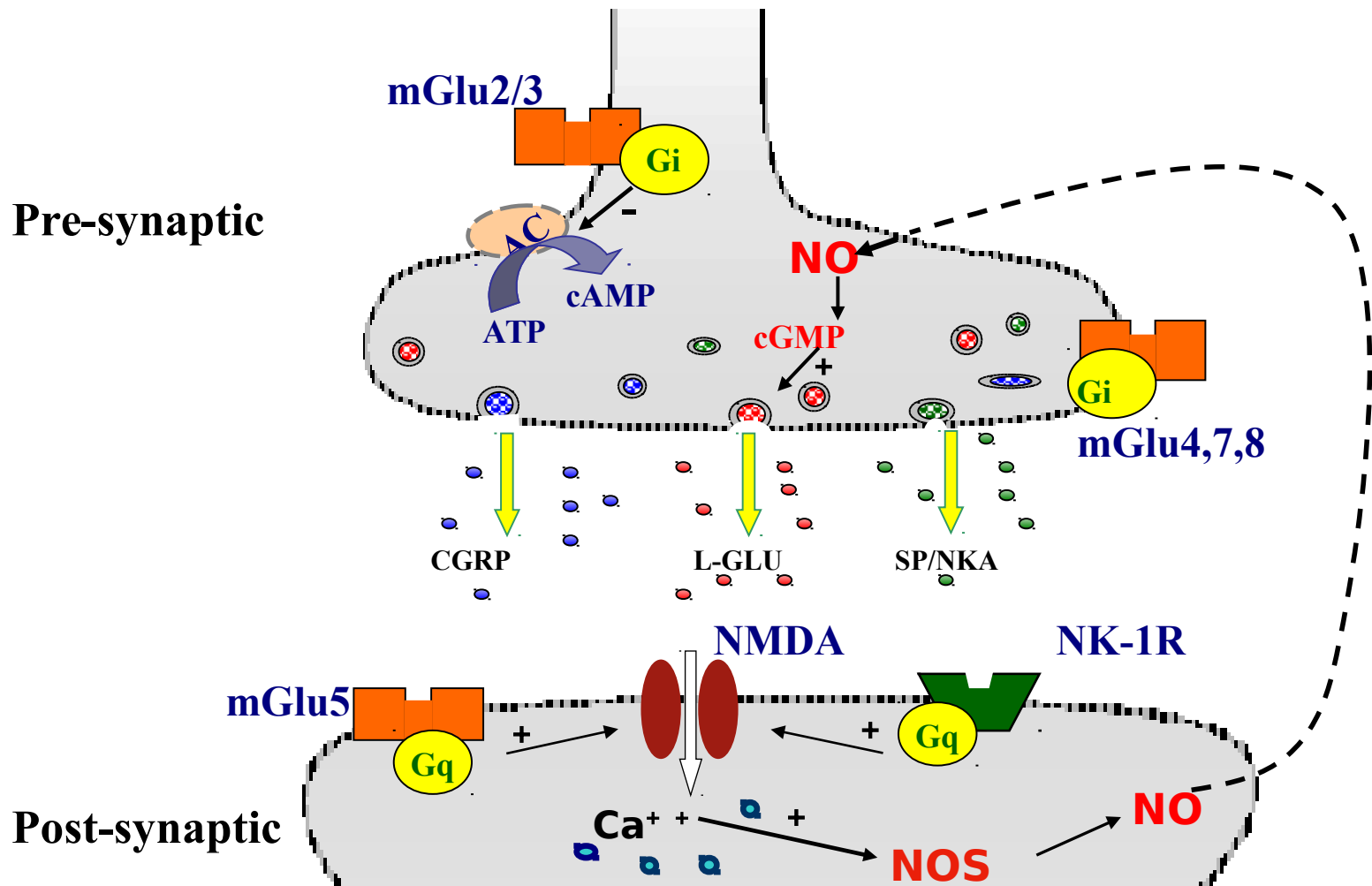
Recettori METABOTROPICI per il GLUTAMMATO (mGluR)

I recettori metabotropici (mGluR) appartengono alla famiglia di recettori associati alle proteine G e mediano l'attivazione di molteplici sistemi di trasduzione fra cui quelli del controllo del dolore.

Attraverso le tecniche di clonaggio molecolare, sono stati isolati i DNA complementari per otto diverse isoforme di tali recettori.

Farmacologicamente tali recettori possono essere suddivisi in tre sottogruppi: il secondo sottogruppo raccoglie i sottotipi mGluR 2 e 3 associati alla inibizione della formazione di AMP ciclico.

Contributo dei recettori mGlu ai processi di informazione nocicettivi



RISULTATI

- Il trattamento con L-acetilcarnitina (LAC) induce analgesia nel dolore acuto e nel dolore cronico
- LAC è l'unico farmaco conosciuto che aumenta i recettori mGlu2
- LAC può essere considerato il prototipo di una nuova classe di farmaci che induce analgesia attraverso la sovraespressione di specifici sottotipi di recettori mGlu

L-acetilcarnitina

**PROFILO
FARMACODINAMICO**

L-acetilcarnitina

L-ACETILCARNITINA

Fornisce gruppi
acetile attivati



Migliora l'attività neuronale
Protegge il DNA mitocondriale
Aumenta la produzione di energia

Maggiore attivazione
recettori per NGF



Miglioramento dei processi
riparatori e del trofismo
cellulare

NEUROPATIA PERIFERICA

L-acetilcarnitina

L-ACETILCARNITINA

Maggiore produzione
di fosfolipidi di
membrana



Migliore stabilità e conducibilità
della membrana neuronale
Migliore attività sinaptica

Maggiore capacità di
rigenerazione assonale
post-traumatica



Migliore recupero della
funzione motorio-sensitiva
del nervo periferico

NEUROPATIA PERIFERICA

L-acetilcarnitina

