

Sharper Mind™ Product Science – Acetyl-L-Carnitine Abstracts

{Note: the underlined sections within the text of the abstracts are highlighted for emphasis by us, not the authors}

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Expert Opin Investig Drugs, 2007 Dec;16(12):1921-31

Natural antioxidants in Alzheimer's disease.

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterised by severe cognitive impairment that ultimately leads to death. Current drugs used in AD are acetylcholinesterase inhibitors and antagonists to the NMDA receptors. These drugs may only slightly improve cognitive functions but have only very limited impact on the clinical course of the disease. In the past several years, based on in vitro and in vivo studies in laboratory animals, natural antioxidants, such as resveratrol, curcumin and acetyl-L-carnitine have been proposed as alternative therapeutic agents for AD. An increasing number of studies demonstrated the efficacy of primary antioxidants, such as polyphenols, or secondary antioxidants, such as acetylcarnitine, to reduce or to block neuronal death occurring in the pathophysiology of this disorder. These studies revealed that other mechanisms than the antioxidant activities could be involved in the neuroprotective effect of these compounds. This paper discusses the evidence for the role of acetylcarnitine in modulating redox-dependent mechanisms leading to the upregulation of vitagenes. Furthermore, future development of novel antioxidant drugs targeted to the mitochondria should result in effectively slowing disease progression. The association with new drug delivery systems may be desirable and useful for the therapeutic use of antioxidants in human neurodegenerative diseases.

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[J Nutr Biochem](#). 2006 Feb;17(2):73-88. Epub 2005 Oct 18.

Acetylcarnitine and cellular stress response: roles in nutritional redox homeostasis and regulation of longevity genes.

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Aging is associated with a reduced ability to cope with physiological challenges. Although the mechanisms underlying age-related alterations in stress tolerance are not well defined, many studies support the validity of the oxidative stress hypothesis, which suggests that lowered functional capacity in aged organisms is the result of an increased generation of reactive oxygen and nitrogen species. Increased production of oxidants in vivo can cause damage to intracellular macromolecules, which can translate into oxidative injury, impaired function and cell death in vulnerable tissues such as the brain. To survive different types of injuries, brain cells have evolved networks of responses, which detect and control diverse forms of stress. This is accomplished by a complex network of the so-called longevity assurance processes, which are composed of several genes termed vitagenes. Among these, heat shock proteins form a highly conserved system responsible for the preservation and repair of the correct protein conformation. The heat shock response contributes to establishing a cytoprotective state in a wide variety of human diseases, including inflammation, cancer, aging and neurodegenerative disorders. Given the broad cytoprotective properties of the heat shock response, there is now a strong interest in discovering and developing pharmacological agents capable of inducing the heat shock response. Acetylcarnitine is proposed as a therapeutic agent for several neurodegenerative disorders, and there is now evidence that it may play a critical role as modulator of cellular stress response in health and disease states. In the present review, we first discuss the role of nutrition in carnitine metabolism, followed by a discussion of carnitine and acetyl-l-carnitine in mitochondrial dysfunction, in aging, and in age-

related disorders. We then review the evidence for the role of acetylcarnitine in modulating redox-dependent mechanisms leading to up-regulation of vitagenes in brain, and we also discuss new approaches for investigating the mechanisms of lifetime survival and longevity.

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Ann N Y Acad Sci, 2005 Aug;1053:153-61

Mechanisms of ischemic neuroprotection by acetyl-L-carnitine.

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Acetyl-L-carnitine is a naturally occurring substance that, when administered at supraphysiologic concentrations, is neuroprotective in several animal models of global and focal cerebral ischemia. Three primary mechanisms of action are supported by neurochemical outcome measures performed with these models and with in vitro models of acute neuronal cell death. The metabolic hypothesis is based on the oxidative metabolism of the acetyl component of acetyl-L-carnitine and is a simple explanation for the reduction in postischemic brain lactate levels and elevation of ATP seen with drug administration. The antioxidant mechanism is supported by reduction of oxidative stress markers, for example, protein oxidation, in both brain tissue and cerebrospinal fluid. The relatively uncharacterized mechanism of inhibiting excitotoxicity could be extremely important in both acute brain injury and chronic neurodegenerative disorders. New experiments performed with primary cultures of rat cortical neurons indicate that the presence of acetyl-L-carnitine significantly inhibits both acute and delayed cell death following exposure to NMDA, an excitotoxic glutamate antagonist. Finally, several other mechanisms of action are possible, including a neurotrophic effect of acetyl-L-carnitine and inhibition of mitochondrial permeability transition. While the multiple potential mechanisms of neuroprotection by acetyl-L-carnitine limit an accurate designation of the most important

mode of action, they are compatible with the concept that several brain injury pathways must be inhibited to optimize therapeutic efficacy.

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Nihon Shinkei Seishin Yakurigaku Zasshi, 2008 Jun;28(3):113-20

[Physiological functions of carnitine and carnitine transporters in the central nervous system]

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L-Carnitine is an essential co-factor in the metabolism of lipids and consequently in the production of cellular energy. This molecule has important physiological roles, including its involvement in the beta-oxidation of fatty acids by facilitating the transport of long-chain fatty acids across the mitochondrial inner membrane as acylcarnitine esters. In the brain, L-carnitine and acetyl-L-carnitine have important roles in cerebral bioenergetics and in neuroprotection through a variety of mechanisms including their antioxidant properties and in the modulation and promotion of synaptic neurotransmission, most notably cholinergic neurotransmission. Acetyl-L-carnitine was successfully applied as pharmacological agents for treatment of chronic degenerative diseases of the senile brain and for slowing down the progression of mental deterioration in Alzheimer's disease, and they may involve both the cholinergic neuronal transmission activity of acetyl-L-carnitine and its ability to enhance neuronal metabolism in mitochondria. Astrocytes are able to produce large amounts of ketone bodies, which are thought to supply adjacent neurons with easily transferable substrates for generation of energy. Thus, the L-carnitine uptake mechanism becomes the rate-limiting step for astrocyte ketogenesis. Several carnitine transporters have been known to be present in peripheral tissues. In this review, the functional expression and physiological role of carnitine transporters in central nervous system is further discussed.

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**[Vitamine-like substances L-carnitine and acetyl-L-carnitine:
from biochemical studies to medicine]**

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Recently reported data clarify our understanding of the molecular aspects of carnitine in medicine. Carnitine is a compound necessary for the transport of acyl-CoA across the inner mitochondrial membrane for their beta-oxidation. Only L-isomer of carnitine is biologically active. The D-isomer may actually compete with L-carnitine for absorption and transport, increasing the risk of carnitine deficiency. By interaction with CoA, carnitine is involved in the intermediary metabolism by modulating free CoA pools in the cell. Detoxification properties and anabolic, antiapoptotic and neuroprotective roles of carnitine is presented. Carnitine deficiency occurs as a primary genetic defect of carnitine transport and secondary to a variety of genetic and acquired disorders. The pathophysiological states associated with carnitine deficiency have been summarized. L-Carnitine is effective for the treatment of primary and secondary carnitine deficiencies. Acetyl-L-carnitine improves cognition in the brain, significantly reversed age-associated decline in mitochondrial membrane potential and improved ambulatory activity. The therapeutic effects of carnitine and acetylcarnitine are discussed.

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