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Review

Potential protective effects of L-carnitine against neuromuscular ischemia-reperfusion injury: From experimental data to potential clinical applications

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SUMMARY

Background & aim: Ischemia-reperfusion (I/R) injury plays important role in morbidity and mortality in several pathologies, including myocardial infarction, ischemic stroke, acute kidney injury, trauma, and circulatory arrest. An imbalance in metabolic supply and tissue's demand during ischemia results in profound tissue hypoxia and microvascular dysfunction. Subsequently, reperfusion further results in activation of immune responses and cell death programs. L-carnitine and its derivatives have been administered to improve tolerance against I/R injury in various tissues. Anti-ischemic properties of L-carnitine and its derivative in neuromuscular organs will be reviewed here at the light of pertinent results from basic and clinical researches.

Method: All available *in vitro* and *in vivo* studies, patents, clinical trials, and meeting abstracts in English language that examined the protective effects of L-carnitine against I/R induced injury in neuromuscular organs were reviewed. Materials were obtained by searching ELSEVIER, web of knowledge, PubMed, Scopus, clinical trials, and Cochrane database of systematic reviews.

Conclusion: Although animal studies on central nervous system and some human studies on muscular system were in favors of effects of L-carnitine against I/R injury, however, more clinical trials are needed to clarify the clinical importance of L-carnitine as a treatment option to manage I/R-induced injury of neuromuscular system.

1. Introduction

Ischemia reperfusion (I/R) injury is a systemic event leading to organ damages due to endothelial dysfunction, free radical production, nitric oxide depletion, and cytokines release [1]. Energy imbalance and changes of cellular homeostasis result in metabolic, functional and structural alterations during ischemia. Over the reperfusion period, calcium influx, release of intracellular enzymes, breakdown of phospholipids and disruption of cell membrane integrity potentiate cell death. These events cause injury to the central nervous system, heart, lungs, gut, kidneys and liver and subsequent risk of mortality and morbidity [2,3].

To reduce I/R injury various therapeutic strategies were investigated at different pathophysiological processes of I/R; mainly physiological and pharmacological free radical scavengers such as L-carnitine [4].

1.1. Mechanisms of I/R injury

Mitochondrial oxidative phosphorylation system consists the electron transport chain (ETC) and ATP synthase. The main role of ETC is transferring electron to electron acceptor O_2. ETC has two main sites for electron entry, complex I (NADH dehydrogenase) and complex II (succinate dehydrogenase). Electrons from each of these two sites are transferred to complex III (bc1 complex) through ubiquinone. Then cyctochrome *c* transfers electrons from complex III to complex IV (cyctochrome*c* oxidase). Cytochrome *c* oxidase transfers electrons to O_2 to convert O_2 and H^+ to H_2O. Pumping H^+ across the inner mitochondrial membrane produces charge difference and electrochemical gradient across inner mitochondrial membrane (mitochondrial membrane potential). This force is utilized by ATP synthase to generate ATP. Under normal conditions the

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electron transport is controlled to reach O_2 and reduce it to H_2O. A small part of electrons escape the ETC to react with O_2 and generate superoxide (O_2^-) as a reactive oxygen species (ROS). Superoxide then reacts with H_2O or H^+ to produce other ROS such as H_2O_2 HO_2 or OH. In addition superoxide reacts with NO to produce a cytotoxic reactive nitrogen species, peroxynitrite. These ROS products are scavenged by antioxidant systems under normal conditions. Ischemia induces major tissue damages. Ischemia insults induce mitochondrial dysfunction by reducing available oxygen and glucose with consequent decreased ATP production. Decreased ATP stimulates glycolytic metabolism of glucose and glycogen. Glucose is metabolized to pyruvate. Pyruvate is then metabolized by lactate dehydrogenase (LDH) to lactate or by pyruvate dehydrogenase (PDH) to acetylCoA. I/R insults (especially reperfusion injury) inhibit PDH activity and increase lactate production and tissue acidosis. I/R insults also inhibit several membrane ion pumps which disturb cellular and mitochondrial gradients and causes cellular influx of Ca^{2+} and Na^+ and efflux of K^+ [5–8].

Mitochondrial membrane potential controls ROS generation. Early after reperfusion, initiation of oxidative phosphorylation and electron transport hyperactivity and hyperpolarization of mitochondrial membrane potential increase ROS production which overcomes endogenous antioxidant systems [9]. ROS generation during ischemia and reperfusion happens through two processes: the xanthine oxidase system in endothelium cells and the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system in neutrophils, the latter is known as the respiratory burst. NO may play protective or damaging role in I/R injury depending on the expression of different isoforms of NO synthase: constitutive NOS (cNOS) or inducible NOS (iNOS). NO production by cNOS have protecting effects including regulation of vascular tone, inhibition of thrombocytes' aggregation and adhesion, inhibiting endothelial adhesion of leukocytes, scavenging free radicals, preserving normal vascular permeability, inhibiting proliferation of smooth muscle cells, stimulating immune system and regeneration of endothelial cells. However, large production of NO by cNOS at the initiation of ischemia results in local depletion of NO precursor, L-arginine. Local L-arginine deficiency restricts longer NO production by endothelium and as a result free oxygen radicals are produced instead of NO. During reperfusion NO production through iNOS expression results in peroxynitrite generation, fat peroxidation, increased free radical production and more I/R injury. Peroxynitrite inactivate critical antioxidant enzyme, superoxide dismutase (SOD) by its nitrating. Peroxynitrite also inhibits glutamate transporters and metabolism leading to neuronal excitotoxicity [10,11].

Neuronal cell death during I/R injury shows varying characteristics in a continuum of necrosis to apoptosis. Ischemia-induced necrosis is the cell death that manifests as cell swelling, depletion of energy stores, cellular membrane disruption that result in changes in fluid status, loss of k^+ and Mg^{2+} and intracellular accumulation of Na^+, Cl^-, H^+, and Ca^{2+} ions. Ischemia-induced anaerobic metabolism produces an intracellular acidosis. Na^+/H^+ exchanger excretes hydrogen ions to buffer intracellular acidosis. This action results in increased Na^+ influx. On the other hand cellular ATP depletion inactivates ATPases such as Na^+/K^+ ATPase that also result in increased intracellular Na^+ concentration. Due to the decreased or reversed Na^+/Ca^{2+} exchanger and decreased Na^+/K^+ ATPase activities, Ca^{2+} efflux and Ca^{2+} reuptake by endoplasmic reticulum decreases. Cellular Ca^{2+} influx happens mainly through ligand-dependent channels (NMDA receptor-gated channels) and partly through voltage-dependent ion channels [12–14].

Increased intracellular Ca^{2+}level is followed by Ca^{2+} sequestration in mitochondria [15]. Increased intracellular Ca^{2+} level activates several intracellular proteases (such as calpains), phospholipase, endonuclease and calmodulin-dependent protein kinases (CaMKs) that induce necrotic cell death [9,14,16]. The C-subunit of the ATP synthase acts as the pore of the mitochondrial permeability transition pore (mPTP). During ischemia decreased adenine nucleotide concentration associates with increased phosphate level that sensitizes mPTP to be opened in response to Ca^{2+}, however, intracellular acidosis prevents mPTP opening. During reperfusion increased ROS production, increased intramitochondrial Ca^{2+} and phosphate levels, depleted adenine nucleotide and rapid return of cellular pH to normal values predispose mPTP to be opened persistently. In addition to its direct effect on mitochondria, intracellular Ca^{2+}also indirectly opens mPTP by activating phospholipase A2.H^+ ions pass through these large pores into the matrix and dissipate mitochondrial transmembrane potential, uncouples ETC and inhibit ATP synthase. Due to osmotic gradient, water enters the mitochondria causing mitochondrial swelling and rupture followed by cytochrome *c* release from mitochondria [9,14,16].

B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax) and Bcl2-associated death promoter (Bad) are pro-apoptotic members of Bcl-2 family that contribute in mPTP formation [12,13]. Increased ROS generation is one effective trigger of Bax gene expression and its translocation from cytosol to mitochondria [17].

Loss of cytochrome *c* causes a shift from aerobic metabolism to anaerobic metabolism and increase in ROS production [8,18]. Therefore, mPTP opening triggers ROS induced ROS release (RIRR), a circle in which ROS facilitate mPTP opening and mPTP opening increase ROS generation. Mitochondrial apoptosis (intrinsic apoptosis) happens by mPTP opening. Cytochrome *c*release following mPTP opening activates caspase 9, caspase 3 and apoptosis [16,19].

Increased intracellular Ca^{2+} concentration also produce calcium pyrophosphate complexes and uric acid, both of them bind to intracellular protein complexes known as inflammasomes and subsequently increase cytokines generation such as interleukine (IL)-1β and tumor necrosis factor (TNF)-α that aggravates I/R injury [14].

1.2. L-carnitine derivatives

L-carnitine (γ-trimethylamino-β-hydroxybutyrate) is a naturally endogenous compound in mammalian cells.L-carnitine exists in the body primarily as its unesterified form, but also as a number of esters including acetyl-L-carnitine (ALC), propionyl-L-carnitine (PLC), and palmitoyl-L-carnitine. Only one-fourth of body store of L-carnitine is endogenously biosynthesized from L-lysine and L-methionine mostly in the liver and kidney, while, the main remaining part is achieved exogenously from dietary sources mainly meat and dairy products [20–24] The main biologic role of L-carnitine is transporting long-chain free fatty acids from cytosol to mitochondria for β-oxidation and producing acetyl CoA to enter tricarboxylic acid cycle. This reaction consumes high oxygen and produces ATP in the processes of ETC and oxidative phosphorylation. At the end of this cycle oxygen concentration decreases by reducing to water and as a consequence ROS formation is also decreases [25]. ALC bypasses PDH (that is inhibited during reperfusion) and donates oxidizable acetyl group to enter aerobic metabolism at a point exactly after the inhibited PDH reaction (Fig. 1) [26].

L-carnitine also increases the activity of antioxidant enzymes such as glutathione peroxidase, catalase, and SOD and also chelates metal ions (*e.g.* ferrous) that catalyze ROS generation. Its antiradical and antioxidant activities are comparable to standard antioxidant agents such as alpha-tocopherol. This antioxidant effect may also decrease I/R injury by ameliorating inhibitory effects of ROS on aerobic metabolism (Fig. 1) [27].

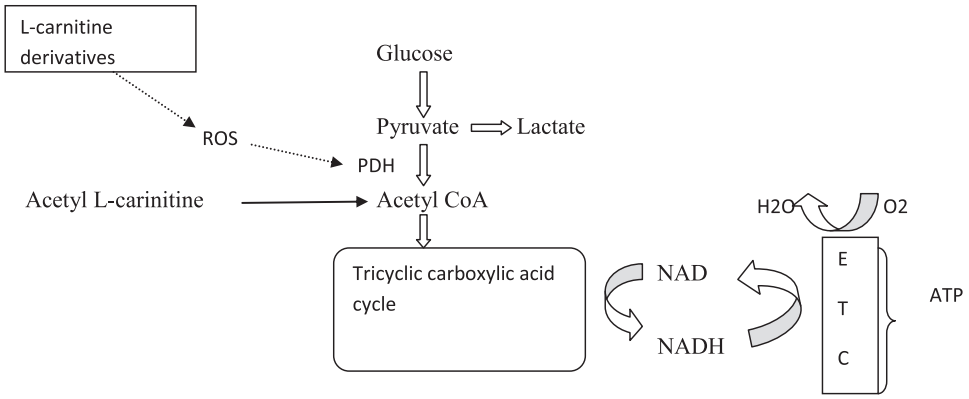

Fig. 1. Acetyl L-carnitine provides acetyl group for acetyl CoA synthesis, thus improving aerobic energy metabolism. ROS inhibit PDH. L-carnitine derivatives scavenge ROS. ECT: electron transport chain. Dash line means inhibitory effect.

This review has focused on protective effects of L-carnitine against I/R injury process in neuromuscular system.

2. Method

We considered all *in vitro* and *in vivo* studies, patents, clinical trials, and meeting abstracts in English language that examined the protective effects of L-carnitine on I/R injury in neuromuscular system. Materials for this review were obtained by searching ELSEVIER, web of knowledge, PubMed, Scopus, clinical trials, and Cochrane database of systematic reviews. Key words used as search terms included "L-carnitine", "L-carnitine derivatives", "ischemia reperfusion injury", "brain", "central nervous system", "spinal cord", "muscle", and "skeletal muscle". This search was performed without time limitation. In each section, studies have been reviewed chronologically.

3. Results

3.1. Carnitine and central nervous system ischemia/reperfusion injury

3.1.1. L-carnitine uptake and functions in neural cells

L-carnitine accumulates in neural cells by active transport through blood–brain barrier by sodium-dependent transporters OCTN2 in brain endothelial cells and ATB, a Na^+-, Cl^--dependent amino acid transporter in the hippocampus [23,28,29]. ALC is a short-chain acylcarinitine. It is a small and water soluble molecule that can be easily transported throughout most body tissues to act as an acetyl donor substance, while, PLC is a long-chain acyl carnitine that needs a transporter to pass the plasma membrane, therefore, have restricted actions compared to ALC [23]. ALC passes blood brain barrier easier than L-carnitine and PLC [30].Adult brain contains 80% free carnitine, 10–15% ALC, and less than 10% long-chain acyl carnitines [23].

L-carnitine derivatives distributes differently in different brain tissue with highest level in the cerebellum and lowest level in the hippocampus and pons [31].

Although fat is not the main fuel for brain and β-oxidation process is low in brain tissues, however, fatty acids can be used by brain tissues especially during fasting and starvation [23].

L-carnitine derivatives modulate neuronal cells' functions by several hypothesized mechanisms such as increasing acetylcholine synthesis by providing acetyl groups, influencing signal transduction pathway and gene expression, stabilizing membrane composition, improving mitochondrial function and antioxidant properties [23,32].

Different acyl carnitines play different roles in the brain. PLC have role in energy metabolism, influencing fluidity and enzyme and transporters activities of the membrane, and modulation of protein and signaling pathways, while ALC improves energy metabolism and membrane stabilization and fluidity, protects neural cells from excitotoxicity, has antioxidant and anti-apoptotic effects, enhances cholinergic neurotransmitter, and modulates protein and gene expression [23].

Studies have shown neuroprotective effect of ALC against age-related learning capacity [33], neurodegenerative disorders such as Alzheimer's disease [34] and brain I/R injury [35].

3.1.2. Carnitine and brain ischemia/reperfusion injury

In contrast to muscular cells that may continue ATP production through glycolytic oxidation during ischemia insult, neuronal cells that are mainly dependent on mitochondrial ATP production undergo main damage [36] Mitochondrial dysfunction and oxidative damage play main roles in the pathogenesis of some neurodegenerative disorders such as Alzheimer's, Parkinson's, Huntington's diseases, and amyotrophic lateral sclerosis [3]. In adult brain ischemia is mainly the result of stroke or cardiac arrest while in infants, complications during delivery may result in neonatal hypoxic-ischemic encephalopathy [9].

Because of high rate of oxidative metabolic activity, relatively low anti-oxidant capacity, low repair mechanism activity and the non-replicating nature of neuronal cell, brain tissues are particularly vulnerable to oxidative injury [14,22,24,36,37].

There are several animal and *in vitro* studies on the potential neuroprotective effects of L-carnitine derivatives against I/R-induced brain injuries [38–48]. These studies have been summarized in Table 1.

These studies suggested that L-carnitine supplementation especially before ischemia insults improve approximately all mitochondrial metabolic and functional changes in brain tissues including cerebral cortex, hippocampus and stratium. However, – well-designed clinical trials are still needed to verify the efficacy of these interventions in human.

3.1.3. Carnitine and spinal cord ischemia/reperfusion injury

Ischemia-induced neuronal damage to the spinal cord especially after operations on the thoracic aorta may induce paraparesis or paraplegia. Mitochondrial dysfunction and oxidative stress have been directly linked to increased excitotoxicity following spinal cord injury. Several mechanisms explain processes that occur

Table 1
A summary of studies on potential protective effects of L-carnitine against central nervous system I/R injury.

Study	Models of studies	Organ Involved	L-carnitine or derivatives administration plan	Monitored indices	Results of L-carnitine derivatives administration
Rosenthal et al. 1992 [38]	Beagles	Brain	ALC 100 mg/kg i.v. followed by 50 mg/kg i.v. every 6 h.	NDS, spectrophotometric and fluorescent assays of frontal cortex lactate and pyruvate levels	Significantly lower NDS and more normal cerebral cortex lactate/pyruvate ratios
Aureli et al 1994 [40]	Fischer rats	Brain	ALC 100 mg/kg i.p. immediately after and again, at 2, 24, 48h following 20 min ischemia	^{31}P and ^{1}H- NMR spectroscopy study	Complete recovery of all metabolites such as inorganic phosphate and ATP, phosphocreatine levels were more elevated and lactic acid content was significantly lower
Shuaib et al 1995 [41]	Gerbils	Brain	ALC 30min before the insult in one set of animals and 30 min after the insult in a second set of animals	Histological evaluation, damage assessment using a 4-point damage score	Significant protection in the cerebral cortex, hippocampus and the striatum
Wainwright et al. 2003 [42]	Wistar rats	Brain	L-carnitine at a dose of 16 mmol/kg i.p. 30 min before the induction of hypoxia	Hemispheric weight assessment, Immunofluorescence detection of dead neurons	Decrease in neurologic injury after both a 7- and 28-d recovery period
Onem et al 2006 [43]	Wistar albino rats	Brain	L-carnitine 100 mg/kg i.v. and vitamin E 50 mg/kg, i.v., alone or in combination after I/R induction	MDA levels, SOD activity, and GSH levels were measured, histopathological examinations under light and electron microscopy	L-carnitine, vitamin E, and combination restored MDA levels and SOD activities, with a tendency to increase surviving neurons in CA1 and CA3 subfield. L-carnitine and vitamin E combination had better GSH levels than treatment of each agents per se
Wainwright et al. 2006 [44]	Wistar rats	Brain	L-carnitine at a dose of 16 mmol/kg i.p. 30 min before the induction of hypoxia	Carnitine, acylcarnitines, and excitatory amino acids by mass spectrometry, carnitine acetyl transferase activity, superoxide, and levels of the mitochondrial phospholipid cardiolipin	Prevention from increase in the ratio of acyl-CoA:CoA, and also in glutamate, glycine, superoxide, and decrease of cardiolipin
Al-Majed et al 2006 [45]	Wistar albino rats	Brain Hippocampus	ALC 300 mg/kg i.p. or PLC 300 mg/kg i.p. for 7 consequent day immediately after the induction of 10 min forebrain ischemia	Histopathological examination and biochemical studies of lipid peroxidation, GSH, total NOx and TBARS concentrations, and ATP production	Either ALC or PLC attenuated ischaemia-induced neuronal damage, manifested by a greater number of intact neurons, ATP and GSH, as well as a decrease in TBARS and NOx
Rau et al. 2007 [46]	Rat hippocampal slice culture model	Brain Hippocampus	5 mM L-carnitine for 2 h prior to oxygen glucose deprivation	Measurement of neuronal population and death by fluorescent microscope, assessment of enzymes such as cleaved caspase-9, cytosolic superoxide, superoxide levels, hydrogen peroxide, SOD, catalase activity	Decrease in superoxide and hydrogen, increase in the expression and activity of SOD and catalase resulted in decreased cell death. Increase in ROS scavenging and the levels of uncoupling protein
Burda et al 2009 [48]	Wistar rats	Brain	Two doses (both 16 mmol/kg i.p., the first 15 min before ischemia and the second just at the onset of reperfusion	Protein synthesis rate, reinitiation ability and neurodegeneration in the frontal cortex and hippocampus by radioactively labeled	Significantly reduction in the I/R induced inhibition of translation and neurodegeneration in the neocortex and hippocampus and dorsolateral striatum
Arduini et al 1990 [52]	Wistar rats	Spinal cord	PLC 100 mg/kg, 30 min before the ischemia induction	Lipid peroxidation indices (the TBARS and conjugated diene content) and intrinsic susceptibility to oxidative stress	Significant decrease of TBARS and conjugated diene production, decrease the intrinsic oxidative susceptibility in the post-ischemicrecirculated tissue
Rahman et al 2001 [53]	Rabbits	Spinal cord	Carnitine 100 mg/kg i.v during ischemia induction	MDA level and histopathological study	Amelioration in both indices
Tetik et al 2002 [54]	Rabbits	Spinal cord	Carnitine 100 mg/kg i.v. during 30 min ischemia induction	Neurological status of 24 and 48 h after operation according to Tarlov's score and histological studies	Improvement in neurological status and histological changes
Darçin et al 2004 [55]	Rabbits	Spinal cord	100 mg/kg L-carnitine infusion over the first 10 min of ischemia or 50 mg adenosine or combination	Tarlov scores for spinal cord function assess and histological studies	Amelioration in both indices combined infusion of adenosine and L-carnitine provided better and complete protection
Akguna et al 2004 [56]	Spraque–Dawley rats	Spinal cord	0.5 mg/kg FK506 i.v., 100 mg/kg L-carnitinei.v, 4 mg/kg azathioprine i.v., 30 min before ischemia induction	Tarlov scores for spinal cord function assess and histological studies	Recovery in that hind-limb motor function and preserved neuron in histopathological finding
Patel et al. 2010 [57]	Female Sprague–Dawley rats	Spinal cord	300 mg/kg ALC i.p, at 15, 30 or 60 min post-injury, followed by one booster after 6 h	24 h post-injury mitochondria assessment for respiration rates, activities of NADH dehydrogenase, cytochrome *c* oxidase and pyruvate dehydrogenase	Increase in respiration rates and amelioration in NADH dehydrogenase, cytochrome *c* oxidase and pyruvate dehydrogenase activity
Karalija et al 2012 [58]	Sprague–Dawley rats	Spinal cord	Continuous intrathecalinfusion of NAC 2.4 mg/day or ALC 0.9 mg/day initiated immediately after spinal injury	Quantitative immunohistochemistry and western blotting for neuronal and glial cell markers, fluorescent tracer studies	Rescue of motoneurones, restored MAP2 and synaptophysinimmunoreactivity, axonal sprouting amelioration but not in reactive astrocytes

ALC: acetyl L-carnitine; ATP: adenosine triphosphate; CoA: Coenzyme A; GSH: glutathione; i.p.: intraperitoneal; I/R: ischemia-reperfusion; i.v.: intravenous; MAP2: microtubular-associated protein-2; MDA: malondialdehyde; NAC:N-acetyl cycteine; NDS: neurological deficit scoring; NMR: nuclear magnetic resonance; NOx: nitrate/nitrite concentrations; PLC: propionyl L-carnitine; ROS; reactive oxygen species; SOD: superoxide dismutase; TBARS: thiobarbituricacid reactive substances.

during the acute phase of spinal cord injury. Initial trauma harms the blood–brain barrier and neuronal tracts and leads to interruptions of blood flow, edema, hemorrhage and retrograde reaction in axotomized neurons. Consequently, pro-inflammatory cytokines, glutamate and ROS are produced in the site of insult resulting to axonal swelling, myelin breakdown, inflammation and mitochondrial dysfunction followed by apoptotic death of neurons and glial cells. In this condition, microglia-generated free radicals and NO also stimulate astrocytes to secrete growth-inhibitory proteoglycans forming the astroglial scar and blocksaxonal regeneration across the lesion site. Prevention of ROS-induced lipid peroxidation appears to be the most important mechanism in protecting the spinal cord from I/R injury [49–51].

There are several animals and one *in vitro* studies on the effects of L-canitine derivatives against I/R-induced spinal cord injury that have been shown in Table 1 [52–58].

These studies reveal that targeting dysfunction of intracellular organs (*e.g.*, mitochondria) may be promising therapeutic optionsin the clinical area for spinal cord injury, as well as other central nervous system injuries. Although carnitine has been used successfully in these conditions, no report on the utilization of carnitine in the prevention of reperfusion injury on the human spinal cord exists.

3.1.4. Mechanisms of L-carnitine derivatives against ischemia/reperfusion injury

Several mechanisms have been proposed for neuroprotective effects of ALC against ischemia insults. The first mechanism is the metabolic hypothesis that is minimizing anaerobic glycolysis. This hypothesis has been supported by reduction in postischemic brain lactate concentrations and elevation of ATP by administration of ALC as an acetyl group donor. ALC exerts this metabolic effect by intra-mitocondrial transferring of acetyl moiety to coenzyme A to generate acetyl CoA. Acetyl CoA is the main substrate for aerobic metabolism. Thereby, ALC helps bypassing metabolic barrier in acetyl CoA production that is induced by ischemic inhibition of PDH (Fig. 1) [3,35,38,59,60]. In contrast to neurons, astrocytes are the main central repositories of glycogen [61]. By stimulating aerobic metabolism, ALC limits post-ischemic needs for high level of glycolysis. Therefore, astrocyte are more susceptible to neuroprotective effect of ALC against brain I/R injury [8].

Since administering ALC several minutes to hours after ischemia insult did not show neuroprotection despite normalization of lactate level in brain tissue, metabolic mechanism cannot be the exclusive mechanism of ALC. The second mechanism is antioxidant effect that is based on reduction in free radicals and increased activity of antioxidant enzymes such as hemoxygenase-1 (HO-1) in brain tissue and cerebral spinal fluid following ALC administration. ALC increases HO-1 gene expression through increased expression of Nrf2, a transcriptional activating factor that stimulates expression of several antioxidant enzymes. The antioxidant mechanism of ALC is partly due to improved brain level of PDH and reduced lactate acidosis, a condition that promotes ROS generation. ALC maintain the redox state of mitochondria/cytosol by modifying glutathione peroxidase/reductase system and thioredox/thioredoxin reductase system. Antioxidant potential of acetyl L-carnitine also up-regulates expression of heat shock protein (Hsp) 60, Hsp 72, and SOD. These changes increase reduced form of glutathione and reverse the inhibition of respiratory complex- IV [3,23]. ALC also decreases 4-hydroxy-2-nonenal generation and protein carbamylation that are indicators of oxidative stress [23].

The third mechanism of ALC is reducing excitotoxicity of neuronal cells by directly antagonizing glutamate receptors, activating of gamma-amino butyric acid (GABA) receptors that make neuronal cells hyperpolarized and resistant to activation by NMDA receptor, and inhibition of secondary events. The main secondary event is activation of mitochondrial permeability transition that results in release of mitochondrial cytochrome *c*, stimulation of ROS production, and desregulation of Ca^{2+} concentrations in neuronal cells. Other proposed neuroprotective mechanism of ALC is inhibition of mitochondrial permeability transition. Carnitine component of ALC has buffering impact on toxic intracellular free fatty acids that are releases by Ca^{2+}-dependent phospholipase 2 during cerebral ischemia and inhibit their effect to provoke mitochondrial permeability transition [3].

ALC may increase nerve growth factor generation and binding [62,63],and improve neuronal cell repair and nerve fiber regeneration [64]. ALC activates phosphoinositol-3-kinase (PI3K)and ERK1/2 pathways that have role in survival and differentiation of neural cells [65]. Additionally, treatment with L-carnitine and acyl carnitines decrease circulating TNF-α and inflammatory interleukins [66].

3.2. Carnitine and skeletal muscle ischemia/reperfusion injury

Ischemia/reperfusion injury in the skeletal muscle is inevitable in many vascular events including thrombolytic therapy, organ transplantation and musculoskeletal traumas. Although skeletal muscle has a higher tolerance to ischemia than other organs, but it has been shown to be the most vulnerable tissue in a limb to ischemia [67]. There are some human and animal studies that have examined the effects of L-carnitine derivatives against I/R muscle injury. These studies have been summarized in Table 2. These studies mainly assessed the role of pre-ischemic treatment with L-carnitine derivatives on muscular morphology, performance, strength, and exercise capacity in muscular I/R injury situations such as patients with intermittent claudication or patients with aortic aneurysm who underwent aortic reconstructive surgery or other muscular ischemia insults [68–74].As seen in Table 2, although some researchers showed promising results [68–71] and proposed administration of L-carnitine derivatives in these patients before ischemia or hypoxia insults such as performing exercise [75,76], however, some other studies showed no effect from pre-ischemia treatment with L-carnitine derivatives on muscular I/R injury [72–74].

As seen, although interest in essential role of L-carnitine in skeletal muscle by translocation of long-chain fatty-acids into the mitochondrial matrix for subsequent β-oxidation and as a regulator of muscle fuel leads to suppose L-carnitineas an interesting substance in muscle performance, conflicting data and paucity of well-designed clinical trials made it soon for exact conclusion.

4. Discussion

Apoptotic cell death during I/R injury was firstly reported 20 years ago in myocardium. Further studies proved the occurrence of both necrotic and apoptotic cell death during I/R injury [77]. Ischemia-reperfusion injury was described as the paradoxical exacerbation of cellular dysfunction or death after restitution of blood flow to the previously ischemic tissues. Salvage of ischemic tissues depends on reestablishment of blood flow in ischemic tissues; however reperfusion itself causes further harm to the ischemic tissue, disturbing function and threatening viability of the organ. Initial ischemia will exert systemic effects on organs and result in multi-system organ failure if it will be profound enough [78]. Organs committed to apoptosis are likely to be reversibly damaged and some of the cells are salvageable by various interventions such as ischemic preconditioning, and pretreatment with antioxidants [77]. Even though the complications that follow reperfusion have been recognized for many years, there is still

Table 2
A summary of studies on potential protective effects of L-carnitine against muscular I/R injury.

Study	Models of studies	Organ involved	L-carnitine or derivatives administration plan	Monitored indices	Results of L-carnitine derivatives administration
Adembri et al 1994 [68]	Human skeletal muscle	Muscle	ALC 2 mg/kg i.v. bolus, followed by 1 mg/kg/min i.v. infusion for 30 min before the clamping of the aorta	Muscle biopsies and blood evaluation for superoxide anion and plasma levels of C3 and C4 complement	Improvement in morphology changes and reduction in activated complement
Brevetti et al 1995 [69]	Human skeletal muscle	Muscle	L-carnitine 500 mg p.o. twice daily; increased at 2-month intervals to 3 g/day in patients showing improvement in treadmill performance	Maximal walking distance, electrocardiographic and routine biochemical and hematologic tests	No changes in electrocardiographic and routine biochemical and hematologic tests, improvement in maximal walking distance
Akar et al 2001 [70]	Rabbit hind limb	Muscle	L-carnitine 100 mg/kg i.v. (total 1.5 ml) and sodium ascorbate 50 mg/kg (total 1.5 ml) 4 h after ischemia induction	Muscle biopsies	Improvement in morphology changes
Andreozzi et al 2002, 2008 [71–75]	Male patients	Muscle	PLC 600 mg i.v. infusion before ischemia induction	Laser-Doppler perfusion units, power spectrum, transcutaneous oxygen pressure and transcutaneous carbon dioxide pressure	Improve in arteriolar function, reducing in acidosis, without affecting in arterial inflow, significant changes inperfusion units and transcutaneous oxygen pressure, increase in mean laser-doppler power spectrum, no significant effects on resting transcutaneous carbon dioxide pressure but significant decrease in transcutaneous carbon dioxide pressure at hypoxia point and during reperfusion
Dutta et al 2008 [76]	Sprague –Dawley rats	Muscle	L-carnitine 100 mg/kg p.o. before induction of 7 day-hypoxia	Mean performed work, time of decay to 50% peak force of contraction, peak force of contraction, mean frequency, plasma CK, lipidhydroperoxide. and TBARS levels	Significant reduction in TBARS, protein carbonyl and lipid hydroperoxide levels and CK activity, no significant improvement in performed work, amelioration in others
Bloomer et al.2010 [72]	Resistance-trained men	Muscle	GPLC 4.5 g/day for 4 weeks	Blood lactate, MDA, F2-iso, H2O2, xanthine oxidase activity, hypoxanthine, total and oxidized glutathione, and trolox-equivalent antioxidant capacity assessment	Oral GPLC supplementation does not attenuate the increase in these biomarkers
Demirel et al 2013 [74]	Fisher rats	Muscle	L-carnitine 100 mg/kg/d i.p. for 7 days before ischemia induction	Fatigue resistance, twitch and tetanic contractions in the EDL and SOL muscles	Increase in tetanic contraction amplitude in the SOL muscles, no changes in fatigue response in any of the muscles

ALC: acetyl L-carnitine; CK: creatin kinase; F2-iso: F2-isoprostanes; GPLC: glycine propionyl- L-carnitine; H2O2: hydrogen peroxide; i.p.: intraperitoneal; I/R: ischemia-reperfusion; i.v.: intravenous; MDA: malondialdehyde; PLC: propionyl L-carnitine; SOL: soleus; TBARS: thiobarbituric acid reactive substances.

confusion on how they are mediated or how they can be prevented or treated.

L-Carnitine was discovered in muscle tissue one hundred years ago. Although skeletal muscle tissues contain more than 95% of the total body's carnitine store but other organs also enriched with it [4]. L-carnitine plays vital metabolic roles; the most well understood is the translocation of long-chain fatty acids into the mitochondria for subsequent β-oxidation and energy production. L-carnitine also improves the turnover of fatty acids peroxydated by free oxygen radicals which are directly involved in oxidative damage of cellular macromolecules such as nucleic acids, proteins and lipids in ischemic tissues [22–24]. Carnitine has been used in different clinical situations as free L-carnitine or its acyl forms mainly ALC and PLC. Acyl L-carnitine derivatives seem to have some tissue specific effects. ALC crosses the blood–brain barrier and shows beneficial effects in brain tissues and neuronal cells in diseases such as neuropathy, depression, fatigue, encephalopathy. PLC is highly specific for cardiac and skeletal muscles and is widely used in cardiac diseases such as ischemic heart disease, hypertrophic heart disease, congestive heart failure and peripheral arterial diseases. Therefore it seems that the clinical findings on one L-carnitine ester cannot easily be generalized to its other esters [22]. Towards the end of the 20th century, a large number of researches were interested in investigating the effects of L-carnitine on preventing I/R damages. Many studies conducted towards protective effects of L-carnitine against I/R-induce heart injury, but other organs meet to these hazards must also be considered. This review was aimed to debate and create a view to manifest the future perspectives of L-carnitine protective effects against I/R injury of neuromuscular systems.

The protective effects of L-carnitine may be related to its ability to decrease oxidative stress by either scavenging ROS or up-regulating antioxidant systems [23]. Most of the evidences originate from animal and *in vitro* cellular models, which make it difficult to extrapolate the results to human subjects.

Most researches used L-carnitine and its derivatives as a supplementation regimen, but routine supplementation in clinical setting must be considered with caution. Of note L-carnitine is not just a cofactor in β-oxidation; it has some other known and yet to be discovered physiologic functions; However, some cautions should be taken to account when applying encouraging animal results in clinical settings. Generally, experimental animal models have been designed to provide informative results by limiting the duration of ischemia, and by utilizing young, healthy and genetically homogenous animals. It is obvious that demonstration of organs protection by any intervention is more challenging in the clinical setting; nevertheless, identification of agents or interventions with potential to protect organs against I/R injury is a clinical wish. .Some possible explanations for failure of experimentally successful antioxidant substances to completely prevent ROS-related I/R injury in clinical setting are very short half-life of ROS that necessitate need for antioxidant with rapid reaction kinetic in clinical setting (not ideal one available yet), multiple sites of ROS generation in I/R-induced damaged organ, restricted cellular uptake of antioxidant agents, and failure of some antioxidant agents to pass blood–brain barrier [9].

Based on this review, almost all animal and *in vitro* studies on efficacy of L-carnitine derivatives against neuromuscular I/R injury showed promising results. Regarding clinical efficacy of L-carnitine derivatives against I/R injury of these organs there are few human studies on muscular but not brain I/R injury. The clinical results of protective effects of L-carnitine derivative against muscular I/R injury is conflicting with possible explanations that have been discussed in previous paragraph. Future, well-designed clinical trials are needed for evaluation clinical efficacy of L-carnitine derivatives on brain I/R injury. For these studies using short-chain esters of L-carnitine such as acetyl L-carnitine is recommended over free L-carnitine or its long-chain esters such as propionyl L-carnitine due to better passing blood brain barrier. These agents seem to be more effective if administered before or soon after initiation of ischemia insult. Administration of L-carnitine derivatives after reperfusion insult suspected not to be effective. Larger clinical trials using enough doses of propionyl L-carnitine before muscular ischemia insult are still needed for confirming clinical efficacy of L-carnitine derivatives in these patients.

5. Conclusion

The assessed role of L-carnitine in CNS organs as a very sensitive ones to ischemia, expanded from neonatal brain hypoxia during delivery to common neurodegenerative disorders such as Alzheimer's or Parkinson's diseases in animal studies. But what we know exactly about L-carnitine' roles in human models is very limited. Regarding the protective effects of L-carnitine against I/R-induced damage, the most evaluated human's organ is muscles. L-carnitine could manifest positive effects on performance, muscle strength and exercise capacity during induced-ischemia conditions but results are conflicting and other studies must be considered.

6. Proposed future research

–Further clinical studies are still needed to determine the appropriate ester type, time, route, dose and duration of L-carnitine administration to prevent muscular I/R injury.

–Positive effects of L-carnitine derivatives against neuronal cells I/R injury in non-human studies must be confirmed in well-designed human clinical trials.

Authors contribution

Both authors were participated in data gathering and manuscript drafting; Simin Dashti-Khavidaki did manuscript finalization.

Conflict of interest

Both authors declare no competing interest and no funding.

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