CINAPS Compound Dossier

(R)-(+-)-Lipoic Acid

11/13/2008
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### I. Compound Information

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<th><strong>Common name</strong></th>
<th>(R)-(+)-Lipoic Acid</th>
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<td><strong>PubChem ID</strong></td>
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<td><strong>Polar surface area</strong></td>
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<td><strong>IUPAC name</strong></td>
<td>5-[(3R)-1,2-Dithiolan-3-yl]pentanoic acid</td>
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<td><strong>Other names</strong></td>
<td>LA; ALA; α-lipoic acid; thiocotic acid; 6,8-dithiooctanoic acid; 1,2-dithiolane-3-pentanoic acid</td>
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<td><strong>Drug class</strong></td>
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<td><strong>Notes</strong></td>
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<td><strong>Development status</strong></td>
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II. Rationale

IIa. Scientific Rationale / Mechanism

Lipoic acid (LA) is a cofactor of mitochondrial decarboxylation enzymatic reactions and is essential for glucose metabolism. With regards to its potential as a therapeutic, LA is a multifunctional antioxidant. The possible antioxidant mechanisms are: (1) scavenging of reactive oxygen species such as superoxide radicals, hydroxyl radicals, hypochlorous acid, peroxyl radicals, and singlet oxygen, (2) generation of other endogenous antioxidants (i.e., glutathione and vitamin E), (3) metal ion chelation, and (4) repair of oxidative damage in macromolecules (Jesudason, 2005).

The reduced form of LA, dihydrolipoic acid (DHLA), is a powerful mitochondrial antioxidant. DHLA can play a role in recycling other cellular antioxidants, including coenzyme Q (CoQ), vitamins C and E, glutathione (GSH). DHLA is also a metal chelator (Liu, 2008).

Another mechanism of the protective effect of LA is mediated through induction of the phase 2 enzyme response through the transcription factor Nrf2, which binds to antioxidant response elements to activate the transcription of phase 2 enzymes, consequently, enhancing the antioxidant defense system (Bilska, 2007; Liu, 2008).

IIb. Consistency

n/a
III. Efficacy (Animal Models of Parkinson’s Disease)

IIIa. Animal Models: Rodent

LA (22 mg/kg, s.c.) coadministered with MPTP (30 mg/kg, s.c.) blocked some of the mechanisms of MPTP toxicity such as activation of the Apoptosis Signal Regulating Kinase 1 (ASK1) and the subsequent downstream kinase phosphorylation. (Such phosphorylation events have been identified as key mediators of cell death in animal models of Parkinson’s disease.) Another mechanism of MPTP/MPP+ induced apoptosis, translocation of Daxx (a transcriptional repressor) from the nucleus to the cytoplasm is blocked by coadministration of LA in mice. Coadministration of LA attenuated MPTP-induced dopaminergic cell loss in the substantia nigra pars compacta as determined by stereological analysis. In animals treated with MPTP alone, 24% of cell loss was seen after 8 days of MPTP, while in animals coadministered LA, the cell loss was only 11%. Coadministration of LA with MPTP also abolished complex I inhibition in striatum and ventral midbrain, another marker for MPTP toxicity (Karunakaran, 2007).

However, repeated treatment with LA (50 or 100 mg/kg, i.p.) over 48 hours had no effect on the 6-OHDA-induced loss of dopamine in striatum or nigral tyrosine hydroxylase positive cells in substantia nigra. LA treatment did not reverse the buthionine sulfoximine (BSO) -induced depletion of glutathione (an early marker of nigral cell death in Parkinson's disease) or prevent the potentiation of 6-OHDA neurotoxicity produced by BSO (Seaton, 1996).

Pretreatment with LA (0.1 mg/kg, i.p.) did not maintain normal dopamine levels in the striatum of MPTP-treated (12 mg/kg, i.p.) mice but did maintain a normal ratio of the reduced to oxidized forms of coenzyme Q in all brain areas tested (Gotz, 1994).

The effect of pre- and post-treatment with LA has been studied in the reserpine PD model in rats. Two injections of LA (50 mg/kg, i.p.) 30 minutes before then 30 minutes after injection of reserpine (5 mg/kg, i.p.) resulted in a significant increase (ca. 30%) in the levels of glutathione (GSH) in the striatum relative to the levels observed in animals receiving reserpine only (Bilska, 2007).


n/a
IV. Efficacy (Clinical and Epidemiological Evidence)

IVa. Clinical studies

n/a

IVb. Epidemiological evidence

n/a
V. Relevance to Other Neurodegenerative Diseases

Since amyloid aggregates have been shown to be stabilized by transition metals such as iron and copper, it has been speculated that LA could either inhibit the formation of aggregates or dissolve existing amyloid deposits. In an *in vitro* experiment, Aβ from human Alzheimer’s Disease (AD) brain and a transgenic mouse model of AD brain could be resolubilized with LA. It was found that cerebral iron levels in old animals fed LA were lower as compared to controls and were similar to levels seen in young rats. These results suggest that LA treatment may modulate the age-related accumulation of cortical iron content, thereby lowering oxidative stress associated with aging (Holmquist, 2007).

The effects of LA supplements in a group of AD patients has been studied. The subjects received the standard treatment of a cholinesterase inhibitor at least 3 months prior to starting LA treatment (600 mg per day, for 48 months, route of administration not specified). The decline in the LA-treated patients appeared to be much slower compared to many other studies published in the current literature (Hager, 2007).

The Tg2576 mouse is a transgenic model of cerebral amyloidosis associated with AD. Ten-month old Tg2576 and wild type mice were fed an LA-containing diet (0.1%) or control diet for 6 months and then assessed for the influence of diet on memory and neuropathology. LA-treated Tg2576 mice exhibited significantly improved learning, and memory retention in the Morris water maze task compared to untreated Tg2576 mice. Twenty-four hours after contextual fear conditioning, untreated Tg2576 mice exhibited significantly impaired context-dependent freezing. LA-treated Tg2576 mice exhibited significantly more context freezing than the untreated Tg2576 mice. Assessment of brain soluble and insoluble α-amyloid levels revealed no differences between LA-treated and untreated Tg2576 mice (Quinn, 2007).

LA improves the cognitive function of senescence accelerated mice. The senescence accelerated prone mouse strain 8 (SAMP8) at 12-months exhibits age-related deterioration in memory and learning, increased levels of beta-amyloid, and oxidative damage to proteins and lipids. Chronic administration of LA improved cognition of 12-month-old SAMP8 mice in both the T-maze footshock avoidance paradigm and the lever press appetitive task without inducing nonspecific effects on motor activity, motivation to avoid shock, or body weight, and reduced oxidative damage to proteins and lipids (Liu, 2008).
VI. Pharmacokinetics

Vla. General ADME

\(R\)-lipoic acid is the endogenous isomer, but the racemate is most often used in the treatment regimen. The drug is partially absorbed in the stomach, and in the proximal portion of the duodenum where uptake is facilitated by carboxylic acid transporters (Carlson, 2007). LA is metabolized by reduction of the disulfide bond, followed by S-methylation, and undergoes chain-shortening by \(\beta\)-oxidation (Teichert, 2003).

Doses of 600-1200 mg are commonly used. As its half life is short (ca. 0.5 h), sustained release formulations have been employed that provide clinically-significant plasma levels for ca. 12 h. Cmax for a 600 mg dose is about 2500 ng/ml, with a Tmax of about 0.5 h (Gleiter, 1999). LA is highly protein-bound (Carlson, 2007). Dose proportionality has been demonstrated for the range 50-600 mg (Breithaupt-Grogler, 1999). Repeat administration did not cause a change in pharmacokinetics (Gleiter, 1996). Coadministration with food causes decrease in AUC of about 20%. The \(R\)-isomer has greater bioavailability, and the \(S\)-isomer may decrease absorption of \(R\) by competition for transport (Carlson, 2007). The literature uniformly notes that LA is well tolerated, and no dose adjustment is needed for renally-impaired patients (Teichert, 2005).

Vlb. CNS Penetration

Panigrahi (1996) demonstrated that, following an intravenous bolus delivered via the saphenous vein (25 mg/kg) LA was detected in cortical samples 1 hour post-dose (2.14 nmol/g wet tissue) and 24 hours post-dose (0.5 nmol/g wet tissue). This CNS penetration is supported by the beneficial effects the authors found in models of cerebral ischemia as well as in the restoration of brain carnitine acetyltransferase reported by Liu (2002) when rats are given supplemental feed containing LA (Panigrahi, 1996; Liu, 2002).

Vlc. Calculated log([brain]/[blood]) (Clark Model): \(-0.87\)
VII. Safety, Tolerability, and Drug Interaction Potential

VIIa. Safety and Tolerability

Clinical trials with LA have highlighted no significant toxicologic effects up to dose levels of 1200 mg/day (Foster, 2007). Adverse events reported related to parenteral administration included gastrointestinal distress, headaches, skin irritation and possible hypoglycemia. Foster suggests that oral LA may present with adverse effects related more to mineral shortages and a need to monitor iron levels. A similarly clean adverse event profile was reported by Evans (2002) in a pharmacokinetic and tolerability study of a novel LA formulation in 21 human, diabetic, patients (Evans, 2002).

This is further supported by the findings in 4-week and 2-year rat toxicology studies (Cremer, 2006a; b). Up to 61.9 mg/kg/day for 4 weeks produced no differences from control in Sprague–Dawley rats, while doses of 180 mg/kg/day for 2 years produced a reduction in food intake with concomitant decrease in body weight. No gross or histopathological changes were observed and relative organ weights were not changed, though there was a significant difference in organ weights between test and control animals owing to the changes in body weight. The rodent NOAEL for LA was deemed to be 60 mg/kg/day from both these studies.

VIIb. Drug Interaction Potential

High doses of LA can result in biotin deficiency and so LA would not be indicated in patients with Vitamin B deficiency that require biotin supplements (Holmquist, 2007).

No citation of drug-drug interactions mediated through competition for metabolism were noted, and it was shown that combination therapy with other diabetes drugs caused no adverse effects and required no adjustment of drug regimen (Gleiter, 1996; Evans, 2002).

In vitro data suggests that there may be an interaction between the mitochondrial actions of LA and valproate (Phua, 2008), however, the relevance of this interaction in the intact animals remains to be demonstrated.
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VIII. Bibliography (cont.)

Gotz, 1994  

Hager, 2007  

Holmquist, 2007  

Jesudason, 2005  

Karunakaran, 2007  

Liu, 2002  

Liu, 2008  

Panigrahi, 1996  

Phua, 2008  
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