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Lipoic acid as an anti-inflammatory and neuroprotective treatment for Alzheimer's disease ☆

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that destroys patient memory and cognition, communication ability with the social environment and the ability to carry out daily activities. Despite extensive research into the pathogenesis of AD, a neuroprotective treatment – particularly for the early stages of disease – remains unavailable for clinical use. In this review, we advance the suggestion that lipoic acid (LA) may fulfil this therapeutic need. A naturally occurring cofactor for the mitochondrial enzymes pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, LA has been shown to have a variety of properties which can interfere with the pathogenesis or progression of AD. For example, LA increases acetylcholine (ACh) production by activation of choline acetyltransferase and increases glucose uptake, thus supplying more acetyl-CoA for the production of ACh. LA chelates redox-active transition metals, thus inhibiting the formation of hydroxyl radicals and also scavenges reactive oxygen species (ROS), thereby increasing the levels of reduced glutathione. In addition, LA down-regulates the expression of redox-sensitive pro-inflammatory proteins including TNF and inducible nitric oxide synthase. Furthermore, LA can scavenge lipid peroxidation products such as hydroxynonenal and acrolein. In human plasma, LA exists in an equilibrium of free and plasma protein bound form. Up to 150 μM, it is bound completely, most likely binding to high affinity fatty acid sites on human serum albumin, suggesting that one large dose rather than continuous low doses (as provided by "slow release" LA) will be beneficial for delivery of LA to the brain. Evidence for a clinical benefit for LA in dementia is yet limited. There are only two published studies, in which 600 mg LA was given daily to 43 patients with AD (receiving a standard treatment with choline-esterase inhibitors) in an open-label study over an observation period of up to 48 months. Whereas the improvement in patients with moderate dementia was not significant, the disease progressed extremely slowly (change in ADAScog: 1.2 points=year, MMSE: −0.6 points=year) in patients with mild dementia (ADAScog<15). Data from cell culture and animal models suggest that LA could be combined with nutraceuticals such as curcumin, (−)-epigallocatechin gallate (from green tea) and docosahexaenoic acid (from fish oil) to synergistically decrease oxidative stress, inflammation, Aβ levels and Aβ plaque load and thus provide a combined benefit in the treatment of AD.

Contents

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1. Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative brain disorder that gradually destroys a patient's memory and ability to learn, make judgments, communicate with the social environment and carry out daily activities. In the course of the disease, short-term memory is affected first, caused by neuronal dysfunction and degeneration in the hippocampus and amygdala. As the disease progresses further, neurons also degenerate and die in other cortical regions of the brain [1]. At that stage, sufferers often experience dramatic changes in personality and behaviour, such as anxiety, suspiciousness or agitation, as well as delusions or hallucinations [2]. AD prevalence in the different age groups is 1% (65–69 years), 3% (70–74 years), 6% (75–79 years), 12% (80–84 years), and 25% (85 and over).

AD is further characterized by two major neuropathological hallmarks. The deposition of neuritic, β-amyloid peptide-containing senile plaques in hippocampal and cerebral cortical regions of AD patients is accompanied by the presence of intracellular neurofibrillary tangles that occupy much of the cytoplasm of pyramidal neurons. Inflammation, as evidenced by the activation of microglia and astroglia, is another hallmark of AD. Inflammation, including superoxide production ("oxidative burst"), is an important source of oxidative stress in AD patients [3,4]. The inflammatory process occurs mainly around the amyloid plaques and is characterized by pro-inflammatory substances released from activated microglia and astroglia [5]. Cytokines are prominent molecules in the inflammatory process, including IL-1β, IL-6, M-CSF and TNF-α [6].

Besides morphological alterations, AD is associated also with a markedly impaired cerebral glucose metabolism as detected by reduced cortical [^{18}F]-desoxyglucose utilization in positron emission tomography of AD patients [7].

2. The cholinergic deficit in Alzheimer's disease

Alzheimer's disease patients show a progressive neuronal cell loss that is associated with region-specific brain atrophy. In particular, the cholinergic projection from the nucleus basalis of Meynert to areas of the cerebral cortex is the pathway that is very early and most severely affected in brains from Alzheimer patients [8]. Loss of basal forebrain cholinergic neurons is demonstrated by reductions in number of cholinergic markers such as choline acetyltransferase, muscarinic and nicotinic acetylcholine receptor binding, as well as levels of acetylcholine (ACh) itself [9]. These changes are highly correlated with the degree of dementia in AD. ACh is derived from choline and acetyl-CoA, the final product of the glycolytic pathway. Pyruvate derived from glycolytic metabolism serves as an important energy source in neurons. Therefore, the inhibition of pyruvate production e.g. by glucose depletion, is considered a crucial factor that leads to acetyl-CoA deficits in AD brains. Based on the findings that a) AD patients have reduced levels of the enzyme choline acetyltransferase and the neurotransmitter ACh compared to healthy elderly people and b) ACh is hydrolyzed by acetylcholine esterase (AChE), acetylcholine esterase inhibitors were the first drug class successfully introduced for the treatment of Alzheimer's patients.

3. Alzheimer's disease — current treatment strategies

At the present moment, only symptomatic treatments with acetylcholine esterase inhibitors are approved for mild to moderate forms of AD. Only one neuroprotective treatment strategy (using the NMDA receptor antagonist memantine) is used in clinical practice, and is approved for moderate to severe forms of AD. The need for a "cholinergic + pro-energetic + neuroprotective" therapy for early stage AD is urgent, and we have proposed that LA is a promising candidate for such treatment [10].

4. LA — a multimodal drug for the treatment of ad

4.1. Possible modes of action of LA interfering with AD specific degeneration

In vitro and *in vivo* studies suggest that LA also acts as a powerful micronutrient with diverse pharmacologic and antioxidant properties [11]. LA naturally occurs only as the *R*-form (RLA) but pharmacological formulations have extensively used a racemic mixture of RLA and *S*-lipoic acid (SLA) in the past before stereoselective synthesis methods became available.

In brief, LA has been suggested to have the following anti-dementia/anti-AD properties:

A) To increase acetylcholine production by activation of choline acetyltransferase,
B) To increase glucose uptake, supplying more acetyl-CoA for the production for acetylcholine,
C) To chelate redox-active transition metals, inhibiting the formation of hydrogen peroxide and hydroxyl radicals,
D) To scavenge reactive oxygen species (ROS), increasing the level of reduced glutathione,
E) To scavenge reactive oxygen species (ROS), down-regulating inflammatory processes,
F) To scavenge lipid peroxidation products and
G) To induce the enzymes of glutathione synthesis and other antioxidant protective enzymes.

These diverse actions suggest that LA acts by multiple mechanisms, both physiologically and pharmacologically, many of which are only now being explored. It has been initially proposed that the reduced form of LA, DHLA, is responsible for many of its pharmacological benefits. However, more and more evidence suggests that many of the "antioxidant" effects of LA *in vivo* are mediated by an indirect effect, in which LA acts as a pro-oxidant and activates the transcription factor Nrf2 which in turn up-regulates the expression of phase II detoxification enzymes as well as antioxidant proteins including glutathione-*S*-transferases, NAD(P)H:quinone oxidoreductase-1, gamma-glutamyl-cysteine synthase, ferritin, and heme oxygenase-1 [12,13].