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Perspectives on the use of lipoic acid in the support of disease treatment*

Perspektywy zastosowania kwasu liponowego we wspomaganiu chorób

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Summary

Lipoic acid (LA) is a natural compound present in food and used as a dietary supplement. LA is endogenously synthesized in small amounts from octanoid acid in the mitochondria. This compound occurs naturally in vegetables such as spinach, broccoli and in animal tissues, in the kidneys, heart and liver. It has been shown that LA is a cofactor in the multienzyme complexes that are responsible for oxidative decarboxylation of α -ketoacids. LA and its reduced form, dihydrolipoic acid (DHLA), have many biological functions leading to a wide variety of actions such as anti-inflammation and antioxidant protection, scavenging of reactive oxygen species, regenerating other antioxidant agents, such as vitamins C and E, and cytosolic glutathione, chelating the transitional metal ions (e.g. iron and copper), and modulating the signal transduction of nuclear factor. Many authors regard LA as a potentially useful agent in the treatment and/or prevention of many diseases such as diabetes mellitus, overweight, obesity, hypertension, heart diseases, inflammation. This review concentrates on the role of LA in the treatment of diabetes mellitus, obesity, inflammation and blood pressure regulation. LA can be considered as a potentially useful drug in treatment of many diseases, particularly those related to excessive production of free radicals.

Keywords: lipoic acid • hypertension • diabetes • obesity • reactive oxygen species

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INTRODUCTION

As for its chemical structure, lipoic acid (LA, 1,2-dithiolane-3-pentanoic acid) is a disulfide derivative of octanoic acid. LA is a naturally occurring short chain fatty acid with sulfhydryl groups. LA as a naturally occurring molecule can be endogenously synthesized from octanoic acid in small amounts in the mitochondria by enzyme lipoic acid synthase [67]. LA naturally occurs in vegetables (spinach, broccoli, tomatoes) and in animal tissues (the kidneys, heart, liver). In the human body LA is synthesized in insufficient quantity and must be absorbed from food [33]. LA may occur in two enantiomeric forms, as R or S; however, only the first one is found in living systems. Pharmacokinetic studies indicate that LA administered orally in doses 50–600 mg was completely absorbed within 30–60 min (half-life of 30 min). LA occurs in tissues in small amounts, because this molecule is rapidly metabolized [61]. Lipoic acid bioavailability is about 30% (range between 20–38%) resulting from major metabolism in the liver (the first-pass effect) [8].

LA and its reduced form, DHLA, are both water- and fat-soluble; therefore, they may act as antioxidants in hydrophilic and lipophilic environments [55]. LA is a cofactor in the multienzyme complexes that are responsible for oxidative decarboxylation of α -ketoacids (it binds to the mitochondrial E2 subunit of α -ketoacid dehydrogenase complexes) such as the pyruvate dehydrogenase complex, the 2-oxoglutarate dehydrogenase complex, the branched-chain oxoacid dehydrogenase complex and the acetoin dehydrogenase complex [1, 69, 72, 74].

LA is a metabolic component of some enzymatic reactions involved in glucose metabolism. It improves glycaemic control and lipid metabolism, reduces blood lipids (total cholesterol, LDL, triglycerides), protects against LDL oxidation [35, 43]. Studies carried out by Jiang et al. [44] demonstrate that LA can restore an impaired brain glucose uptake, mitochondrial bioenergetics and synaptic plasticity in an aging brain through the modulation of insulin signaling.

Moreover, supplementation of LA improved cognition and memory deficits in the aged SAMP8 mice and aged rats [29] and reduced hippocampal-dependent memory deficits in the Tg2576 transgenic mouse model of Alzheimer's Disease (AD) [73, 97] indicate that LA supplementation inhibits hyperphosphorylation of Tau (microtubule-associated protein) and neuronal loss including ferroptosis (iron- and ROS-dependent cell death). It has been indicated that the level of LA declines remarkably with age, which may lead to endothelial dysfunction. LA and DHLA improve endothelial function and blood flow. Endothelial cells play an important role in vascular tone regulation, hemostasis, fibrinolysis and in the production of several substances such as endothelin or nitric oxide [7, 79]. It has been shown that LA supplementation improves the function of the endothelium in young people with type 1 diabetes [79]. Endothelial

dysfunction may result in the development of atherosclerosis [16, 89]. Moreover, LA enhances mitochondria expression of key antioxidant enzymes and accelerates glutathione synthesis, which plays a crucial role in preventing damage of important cellular components caused by ROS [38, 63, 64, 71]. LA as a potent mitochondrial antioxidant compound has anti-inflammatory and antithrombotic properties and exerts a positive impact on the nitric oxide-mediated vasodilatation [38].

Actually, there has been increasing interest in the potential therapeutic uses of pharmacological doses of free alpha-lipoic acid [17, 20, 70].

ANTI-OXIDATIVE AND ANTI-INFLAMMATORY EFFECTS OF LA

Both LA and DHLA behave like a free radical scavengers of reactive nitric species (RNS) and reactive oxygen species (ROS) which are by-products of oxidative metabolism. ROS include free radicals, such as superoxide ($O_2^{\bullet-}$), hydroxyl (OH^{\bullet}), peroxy (RO_2^{\bullet}), and hydroperoxy (HRO_2^{\bullet}), and non-radical species, such as hydrogen peroxide (H_2O_2) and hydrochloric acid (HCl). Among RNS there are e.g. nitric oxide (NO^{\bullet}), nitrogen dioxide (NO_2^{\bullet}), nonradical peroxynitrite ($ONOO^-$), nitrous oxide (HNO^{\bullet}), and alkyl peroxy nitrates ($RONOO^{\bullet}$) [77, 86]. Macromolecules such as lipids, proteins and DNA can be damaged by increased levels of these species. Therefore, scavenging activity of LA can decrease oxidative stress (an imbalance of oxidant and the anti-oxidant capacity) [94]. Apart from ROS scavenging capacity, LA has the ability to regenerate reduced forms of other antioxidants (vitamins C and E, coenzyme Q10, glutathione). It also acts as a heavy metal chelator against iron and copper, lead, cadmium and mercury [68]. LA supplementation (500 mg/kg b.w. for 28 days) in broilers exposed to oxidative stress by dexamethasone enhanced total antioxidant capacity and increased activity of superoxide dismutase (SOD), glutathione peroxidase (GPX) enzymes and decreased plasma level of MDA (malondialdehyde) and mRNA gene expression of interferon gamma (IFN- γ), interleukin 1beta (IL-1 β), interleukin 6 (IL-6) [26]. Moreover, LA proved to be more effective in normalizing the oxidative stress than vitamin C or vitamin E [26]. Owing to these properties, it has the ability to repair oxidative damage. Antioxidant properties of lipoic acid are mediated by nuclear factor kappa-light chain-enhancer of activated B cells (NF- κ B) and nuclear factor erythroid 2-related factor 2 (Nrf2) [21, 49, 91]. Antioxidant properties of LA involve inhibiting the degradation of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IKB α) by the compound, and thus inhibiting the activation of NF- κ B pathway in human umbilical vein endothelial cells (HUVECs), as well as inhibiting the expression of vascular cell adhesion molecule 1 (VCAM-1) and cyclooxygenase 2 (COX2) [91]. The anti-inflammatory effect of LA is connected with the elevation of intracellular levels of Nrf2 that occurs through independent mechanisms, by breaking links between Nrf2 and Keap 1 (Kelch ECH

associating protein 1). These actions lead to decreased expression of various pro-inflammatory cytokines, such as TNF- α , IL-6, IL-1 β , and increased expression of enzymatic antioxidants, such as glutathione peroxidase, superoxide dismutase and heme oxygenase [34, 35, 78, 80]. It also stimulates the release of IL-10, anti-inflammatory cytokines [13, 85]. It can also decrease prostaglandin E2 (PGE2) and NO levels by means of COX-2 and nitric oxide synthase inhibitor (iNOS) inhibition [53].

Anti-inflammatory properties of lipoic acid were analyzed by many authors. Carbonelli et al. [12] studied a group of Caucasian subjects who followed a normal diet with LA supplementation (800 mg/d) for four months. The study results showed a decrease in the concentration of c-reactive protein (CRP) and TNF- α in obese subjects. Other authors also proved that LA supplementation triggered changes in inflammatory markers – a decrease in TNF- α , IL-6, CRP, total lymphocytes and an increase in adiponectin [42, 96]. On the contrary, Mohammadi et al. [62] found that LA supplementation had no significant effect on IL-6 and CRP levels.

LIPIC ACID AND BLOOD PRESSURE

Hypertension is defined as abnormally high blood pressure (BP) above 130/70 mmHg. People with high blood pressure are at risk of developing stroke, heart diseases, diabetes and kidney failure. Studies indicate that increased production of ROS may be connected with certain diseases of the cardiovascular system including high blood pressure [3]. Therefore, oral supplementation with antioxidants such as LA may be a useful alternative treatment of high BP. Results of studies on the effects of LA on blood pressure are inconsistent. Mohammadi et al. [62] indicated that LA administration at a dose of 600 mg/day for 12 weeks in male patients with chronic spinal cord injury caused a significant decrease in both systolic blood pressure (SPB) and diastolic blood pressure (DBP). Similarly, Mazloom and Ansar [5] showed that the administration of LA, a dose of 300 mg/day, for eight weeks in type 2 diabetic patients resulted in a significant drop in SPB and DBP.

McMackin et al. [57] showed that combined therapy including lipoic acid (200 mg/day) and acetyl-L-carnitine (500 mg/day) caused a decrease in blood pressure in patients with coronary disease and blood pressure above the median (from 151 \pm 20 to 142 \pm 8 mmHg), as well as in patients with the metabolic syndrome (from 139 \pm 21 to 130 \pm 18 mm Hg). Vasdev et al. [87] in studies on hypertensive rats indicated that dietary LA supplementation (500 mg/kg b.w. of feed) for 9 weeks caused a significant reduction in blood pressure. A study on hypertensive rats on high salt diet showed that LA supplementation for 8 weeks decreased the mean arterial pressure (MAP), plasma level noradrenaline and enhanced intracellular antioxidant capacity [40]. Cheserek et al. [15], in their study on mice on high fat diet, also indicated that LA supplementation significantly decreased blood pressure

and enhanced antioxidant capacity. Dudek et al. [22] in their studies on normotensive rats reported that a single dose of LA (50 mg/kg b.w. *ip*) resulted in a significant decrease in SBP and DBP. This effect was associated with the inhibition of an ATP-dependent potassium channel by glibenclamide. Ergur et al. [27] administered LA at a dose of 100 mg/kg b.w. in the remnant kidney model and observed a decrease in blood pressure and ameliorated histomorphological changes in the abdominal aorta. El Midaouri et al. [25] administered LA at a dose of 500 mg/kg b.w. for three weeks to Sprague-Dawley rats that were on a glucose diet and showed that LA resulted in a decrease in arterial pressure and aortic basal oxygen production. Yu et al. [93] reported that a dietary LA supplement administered for 3 weeks prevented an elevation of SPB. Also, other researchers found that LA attenuated blood pressure increases in a remnant kidney model [58]. In another study, de Champlain et al. [19] suggested that the development of hypertension may be totally prevented or markedly attenuated by chronic treatment of LA. Many of the papers did not show any clear LA action on blood pressure. Huerta et al. [41] in studies on healthy women indicated that 0.3 g/day LA for 10 weeks had no influence on blood pressure. Rahman et al. [75] evaluated the effects of quinapril plus 600 mg LA for 8 weeks in type 2 diabetes mellitus with stage 1 hypertension and reported no effects for LA on SBP and DBP. Koh et al. [48] investigated the effects of LA at a dose of 1800 and 1200 mg for 20 weeks in obese or overweight subjects with hypertension, diabetes mellitus, or hypercholesterolemia and reported no significant effect for blood pressure with both doses.

Similarly, other authors observed no significant effect of LA supplementation in different doses on blood pressure [54, 81]. The results of parallel-designed studies are inconsistent.

LIPIC ACID AND DIABETES

Diabetes is a syndrome of various symptoms caused by insulin deficiency and biochemical abnormalities, of which two are essential: a/limited glucose passing to multiple “peripheral” tissues, b/increased release of glucose from the liver into the blood. These disorders lead to an increase in excess glucose in the extracellular space and to glucose deficiency in many cells. It was shown that hyperglycemia generates ROS and RNS and contributes to the development and progression of diabetes complications. In diabetic patients, hyperglycemia triggers damage to the endothelial cells causing their dysfunction which impairs endothelial nitric oxide synthase (eNOS) activity, thus increasing ROS production, with consequent reduction of NO bioavailability. Chronic elevation of glucose in the cellular “milieu” facilitates the formation of advanced glycation end-products (AGEs), which directly disrupts the function of multiple essential cellular and extracellular proteins such as: tubulin, actin, laminin. Moreover, AGEs activate a specific receptor (the receptor for AGEs or RAGE), and their interaction produces pro-inflammatory and pro-

oxidative effects in peripheral nerves [84]. Babizhayev et al. [6] indicated a strong relationship between severity of diabetic neuropathy and frequency and duration of hyperglycemic periods. The incidence of diabetes is also linked to aging, adoption of western lifestyle, physical inactivity and obesity [14]. Type 2 diabetes mellitus is regarded as a risk factor for cardiovascular and nervous diseases. Application of an antioxidant such as LA may appear to be a promising strategy for diabetes treatment. In patients with type 2 diabetes, LA may influence angiogenesis through an impact it has on some circulating factors including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), monocyte chemoattractant protein 1 (MCP-1), as well as IL-10 [24].

LA shows positive effects in diabetes because of its insulin-mimetic (regulating the), insulin-receptor/phosphatidylinositol 3 – kinase pathway (IR/PI3K/pathway) and anti-inflammatory properties and participation in mitochondrial bioenergetic reactions [45, 76]. LA is a key cofactor for mitochondrial bioenergetic enzymes, including pyruvate dehydrogenase and α -ketoglutarate dehydrogenase complexes, stimulating glucose and lipid metabolism [10].

Jacob et al. [43] showed that LA as a powerful antioxidant, improved insulin sensitivity in patients with type 2 diabetes. In addition, it has been proved that LA prevents development of insulin resistance and arterial hypertension as well as a decrease in the body weight in rats that are chronically fed with glucose [25, 59]. Derosa et al. [20] indicated that lipoic acid supplementation improved lipid profile, glycemic control, markers of oxidative stress such as MDA, SOD, GSH-Px and inflammatory CRP. Moreover, LA not only alleviates oxidative stress in hippocampus but also causes better learning skills in rats with streptozotocin-induced diabetes [95]. In streptozotocin-induced rats LA treatment can protect against impaired vascular responsiveness [67, 79].

LA is commonly used as a strong antioxidant in the treatment of diabetic polyneuropathy. In the SIDNEY trial it was shown that oral treatment with LA administered for five weeks caused an improvement of neuropathic symptoms in patients with distal symmetric polyneuropathy [99]. Also, other investigators indicated that LA applied at a dose of 300–600 mg *iv*/day for 3 weeks had a positive effect on nerve conduction velocity [37].

It was shown that, following cerebral ischemia in rats, neuroprotective and neurorestorative effects of LA are mediated *via* insulin receptor activation [16]. The previous study reported that LA is safe and remarkably reduces oxidative stress levels in elderly patients with diabetes mellitus complicated by acute ischemic stroke [98]. Choi et al. [17] indicated that LA applied in patients with acute ischemic stroke (AIS) and diabetes resulted in a decreased risk of neurological deterioration and hemorrhagic transformation. Apart from its positive effects on therapy of diabetic neuropathy, LA

may also be useful in the treatment of vascular complications and nociception in type 2 diabetes [18, 83]. In the study on mice it was indicated that LA in combination with other compounds may exert a more powerful effect on the treatment of neural complications of type 2 diabetes [36, 45, 92]. Some authors reported that favorable results following LA treatment in diabetic polyneuropathy may remain even for 4 years [4, 77, 100].

LA was also able to reduce the body weight in obese diabetic rodents by suppressing food intake and increasing energy expenditure. Moreover, in skeletal muscle and pancreatic islets, LA reduced the accumulation of triglyceride. The effects indicate that LA prevents diabetes mellitus in obese diabetic rats by reducing lipid accumulation in both non-adipose tissue and adipose tissue [82].

Other papers do not confirm the positive effect of LA in diabetes. Miadaoui et al. [60] indicated that LA treatment did not affect hyperglycemia, hyperinsulinemia and insulin resistance in Zucker Diabetic Fatty rats. These findings correspond to the study which showed that LA did not reduce an increase in the blood glucose levels and insulin resistance in obese female Zucker rats [65].

LIPOIC ACID AND OBESITY

Obesity is defined as abnormal or excessive fat accumulation that involves a risk to health. The main cause of overweight/obesity is a positive energy balance in which energy intake exceeds energy expenditure over a prolonged time, leading to increased body mass including accumulation of subcutaneous and visceral fat [28, 55]. Clinically, in adults, obesity is defined as having a body mass index (BMI) over 30, specifically, with an abnormal fat distribution. Normally, adipose tissues are present in peripheral adipose tissues such as hip and gluteofemoral fats and central adipose tissues such as visceral and upper abdominal subcutaneous fats [51]. The adipose tissue is heterogeneous and includes vascular cells, adipocytes and immune cells [51]. Moreover, this tissue stores energy and lipids in the form of triglycerides [23, 46, 84, 85] and is an endocrine organ that secretes a large variety of adipokines [33]. The increase of obesity prevalence may be associated with excessive intake of energy-rich diets and a sedentary lifestyle. Several studies have also shown that obesity may be a result of epigenetic change [9, 11, 56]. Many factors such as nutrition, inflammation, physical activity, oxidative stress, hypoxia, smoking, sex or age induce changes in the epigenome and contribute to its plasticity through life [52, 56, 61].

Obesity is very serious problem, not only in terms of aesthetics but also health. It influences the development of various diseases such as hypertension, metabolic syndrome, coronary heart disease, type 2 diabetes and reproductive problems [90]. Some authors believe that the accumulation of fat in obesity is associated with low-grade inflammation or oxidative stress. In obese patients with impaired glucose tolerance and dyslipi-

demia, short-term treatment with LA (600 mg iv day for a period of 2 weeks) improved insulin sensitivity and the lipid profile and decreased the levels of MDA, 8-isoprostaglandin, TNF- α , and IL-6 [96]. The accumulation of visceral fat may contribute to systemic changes, such as impairment in insulin signaling and the development of atherosclerosis. [2, 31]. The pro-inflammatory conditions and oxidative stress induced by an increase in adiposity amounts in obesity are two inter-linked factors which may play an important role in the occurrence of obesity-related metabolic comorbidities [32]. Obesity is associated with an enhanced number and size of triglyceride-filled white adipocytes [23].

It has been suggested that dietary supplements in the form of bioactive compounds such as alfa-lipoic acid may lessen the negative health effects of obesity [30, 41]. LA supplementation (separately or in combination with eicosapentaenoic acid – EPA) at a low dose of 300 μ g/day may help to promote weight loss and to reduce fat mass in healthy obese women following a hypocaloric balanced diet. This report also showed that LA alone or in EPA+LA combination resulted in a drop of leptin level parallel with a reduction of fat mass. A decrease in leptin level during weight loss process may be caused by a decrease in the metabolic rate [39]. In other studies, Koh et al. [48] found that, together with an energy-restricted diet in overweight and obese subjects, LA supplementation at doses of 1200–1800 mg/kg/day contributed to weight loss, the reduction of BMI and waist circumference, but only at the highest dose tested. Carbonelli et al. [12] indicated that

LA supplementation at a dose of 800 mg/day for four months reduced weight, BMI and abdominal circumference in overweight and obese subjects. This report suggests that these effects may be associated with increased satiety induced by LA. Also, Namazi et al. [66] performed a meta-analysis which showed that LA supplementation with LA caused a significant but slight decrease of body weight and BMI in obese individuals; however, a safe dose of LA should not exceed 1200 mg/day.

Also, early studies in animal models have suggested that LA promotes weight loss by reducing food intake and stimulating energy expenditure [72, 88]. Such effects may be associated with the suppression of hypothalamic activated protein kinase (AMPK) activity triggered by LA [47, 72].

Literary sources show that treatment with LA results in small yet significant short-term weight loss as compared to placebo. Further research is required to examine the effect of different doses and long-term benefits of LA for weight management [50].

CONCLUSION

LA can be considered as a potentially useful supplement in the treatment of many diseases, especially those related to excessive production of free radicals. Application of LA may turn out to be a promising strategy for diabetes and atherosclerosis treatment. Treatment with LA also results in a small yet significant short-term weight loss.

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