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Review Article

α-Lipoic Acid: A Multifunctional Antioxidant That Improves Insulin Sensitivity in Patients with Type 2 Diabetes

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ABSTRACT

α-Lipoic acid (LA) is a disulfide compound that is produced in small quantities in cells, and functions naturally as a co-enzyme in the pyruvate dehydrogenase and α-ketoglutarate dehydrogenase mitochondrial enzyme complexes. In pharmacological doses, LA is a multifunctional antioxidant. LA has been used in Germany for over 30 years for the treatment of diabetes-induced neuropathy. In patients with type 2 diabetes, recent studies have reported that intravenous (i.v.) infusion of LA increases insulin-mediated glucose disposal, whereas oral administration of LA has only marginal effects. If the limitations of oral therapy can be overcome, LA could emerge as a safe and effective adjunctive antidiabetic agent with insulin sensitizing activity.

GENERAL OVERVIEW OF α-LIPOIC ACID

In 1937, a component of potato extract, named "potato growth factor," was discovered to be necessary for the growth of *Lactobacillus*.[1] Subsequent work by a number of laboratories led to the isolation and purification of the active compound in 1951.[2] The compound was identified as α-lipoic acid (LA; occasionally referred to as thioctic acid), an eight-carbon disulfide containing a single chiral center (Fig. 1). LA is reduced *in vivo* to its dithiol form, dihydrolipoic acid (DHLA), a compound that also possesses biological activity.[3]

LA is synthesized in organisms ranging from bacteria to man. In humans, it is synthesized in liver and other tissues, where it functions as a natural co-factor in multienzyme dehydrogenase complexes, such as pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase.[4] Pyruvate dehydrogenase is localized in mitochondria where it catalyzes the oxidative decarboxylation of pyruvate to acetyl-CoA, a critical step in oxidative glucose metabolism.[5] In the PDH complex, LA is covalently attached to a lysine side chain of the dihydrolipoyl transacetylase component (E_2), where it forms the lipoamide prosthetic group that accepts an acetyl group and transfers it CoA. Thus, LA plays an essential role in mitochondrial-specific pathways that generate energy from glucose.

LA and DHLA are also potent antioxidants.[6] As shown in Figure 2, four distinct antioxidant actions of LA and DHLA have been observed: (1) reactive oxygen species (free radical) scavenging activity, (2) capacity to regenerate endogenous antioxidants such as glutathione, vitamin C and vitamin E, (3) metal chelating

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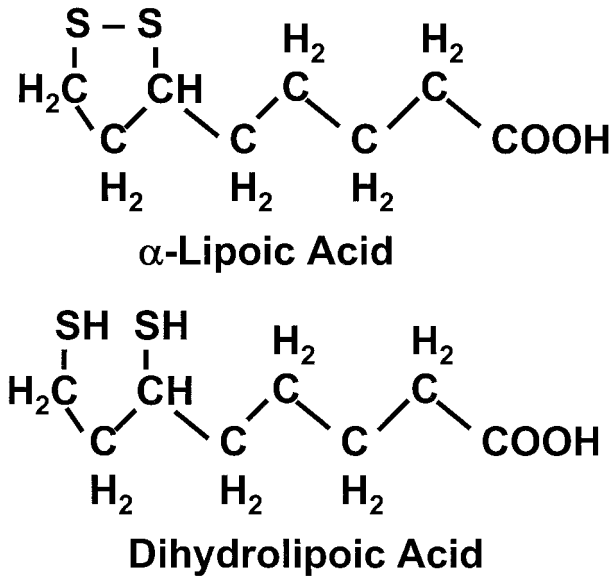

FIG. 1. Chemical structures of α-lipoic acid and dihydrolipoic acid. α-Lipoic acid is an eight cabon disulfide compound containing a single chiral carbon. It is readily reduced *in vivo* to its dithiol form, dihydrolipoic acid. The R-enantiomer is the naturally occurring form of α-lipoic acid, while synthetic α-lipoic acid is a racemic mixture containing both the R- and S-enantiomers.

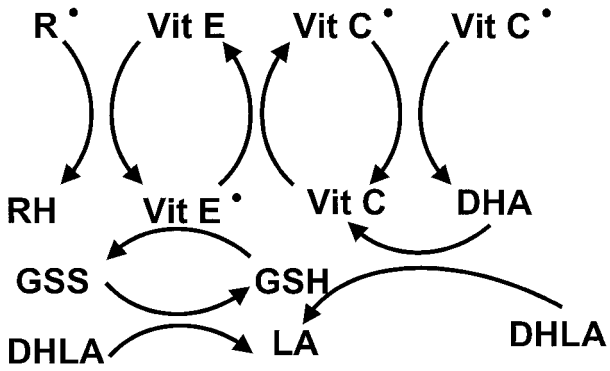

FIG. 3. Regeneration of endogenous antioxidants by α-lipoic acid and dihydrolipoic acid. The regeneration of endogenous antioxidants occurs through a cooperative set of reactions that can involve many substances. Shown here is a highly simplified example of how α-lipoic acid (LA) and dihydrolipoic acid (DHLA) are capable of interacting with dihydroascorbate (DHA), vitamin C (Vit C), glutathione (oxidized, GSS; reduced, GSH) to regenerate vitamin E (Vit E). LA after reduction to DHLA is able to facilitate the nonenzymatic regeneration of vitamin C and GSH, both of which are able to regenerate vitamin E. Reducing equivalents for the conversion of LA to DHLA are provided by NADH or NADPH (not shown). R•, Vit C•, Vit E• = charged species

activity, and (4) repair of oxidized proteins.[4,6] LA and DHLA function as a redox couple to regenerate endogenous antioxidants through a cooperative set of reactions. Figure 3 shows a simplified example of their interaction with vitamin C and glutathione to regenerate vitamin E. The ability of LA to regenerate glutathione may have particular physiological significance, as glutathione is the major intracellular thiol antioxidant. It facilitates the protection of redox-sensitive proteins during periods of increased oxidative stress. In addition to the ability of LA to regenerate existing glutathione, there is evidence that LA and DHLA are able to increase its *de novo* synthesis.[7]

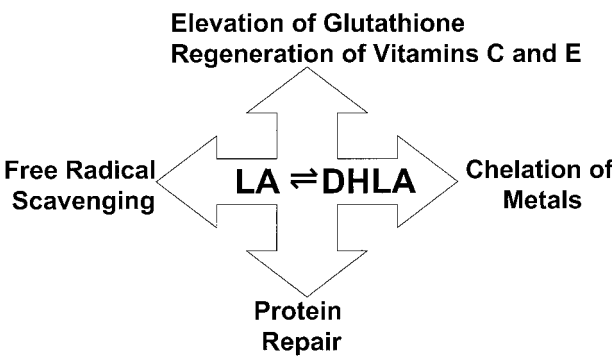

FIG. 2. Antioxidant functions of α-lipoic acid and dihydrolipoic acid. Four general functions related to antioxidant activity have been ascribed to α-lipoic acid (LA) and its dithiol form, dihydrolipoic acid (DHLA). With regard to protein repair, certain amino acids including methionine, cysteine, tyrosine, and others are highly susceptible to oxidation, which can result in loss of function. LA (through DHLA) supplies reducing equivalents to facilitate endogenous enzymatic systems in the repair (reduction) of oxidized residues. Comprehensive descriptions of each of these functions have been reviewed elsewhere.[4,6]

LA is soluble in lipid and aqueous environments. Because LA is lipid soluble, it is highly effective at reducing free radicals, including lipid peroxides, in cellular membranes. Because LA is also water soluble, it is able to gain access to the cytosol, where it effectively scavenges free radicals at their mitochondrial source.[4]

MITOCHONDRIA, FREE RADICALS, AND OXIDATIVE STRESS

Free radicals are highly reactive molecular by-products produced in all cells as a result of normal metabolism, aging, and disease.[8–10] Because of their essential role in cellular metabolism, mitochondria are the chief sources of free

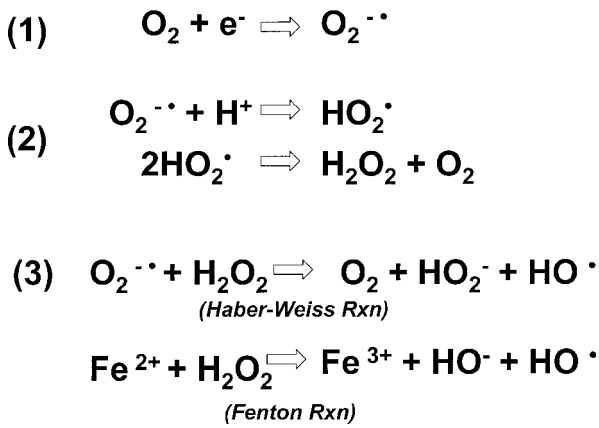

FIG. 4. Selected examples of oxygen free radicals. (1) Superoxide anion is formed when molecular oxygen acquires an additional electron, (2) hydrogen peroxide can be generated by several metabolic reactions, (e.g., from superoxide), and (3) hydroxyl radicals can be formed from either the superoxide anion or from hydrogen peroxide.

radical production.[10,11] Mitochondria are the sites of electron transport, the process of passing electrons through the respiratory chain of proteins located in the inner mitochondrial membrane. This creates a transmembrane pH gradient that drives the production of ATP. This occasionally results in an electron bonding to an oxygen molecule outside the respiratory chain. This single reduction, or transfer of a single electron, creates a molecule with unpaired electrons, referred to as a free radical (Fig. 4). There is an inherent inefficiency in the process of transferring electrons through the chain, which increases with age and disease.[10,12] Thus, aging and disease are associated with increased levels of free radicals,[8,9] a condition known as oxidative stress.[13]

Excessive production of free radicals, or their inadequate neutralization by antioxidants, leads to the damage of proteins, lipids, and DNA. Because of their proximity to the source of free radical production, mitochondrial constituents become primary targets of free radical damage. For example, it has been estimated that an individual produces approximately 1 kg of oxygen radicals per year, the consequence of which is approximately 100,000 oxidative "attacks" on mitochondrial DNA per cell each day.[10] The cumulative and inevitable effect of these "attacks" on mitochondrial DNA is an increased frequency of mutations,[14] which likely results in the production of proteins with impaired function.

Because of the fundamental role that that mitochondria play to fulfill physiological energy requirements, and the pathological repercussions that occur when this function is challenged, the pharmacological use of antioxidants is often recommended as an approach to supplement endogenous defenses.[10] There are experimental data to indicate that LA acts as an effective protective agent for mitochondria. In rats, LA can partially reverse the decline in mitochondrial function and increase in oxidative stress associated with aging.[15,16] In these studies, LA treatment also reversed the age-associated decline in glutathione content, and attenuated the age-associated rise in lipid peroxidation.

OXIDATIVE STRESS AND DIABETES

It is clear that increased oxidative stress is associated with a variety of pathological conditions including diabetes, atherosclerosis and cardiovascular disease, and neurodegenerative diseases (Fig. 5).[9,17–22] Oxidative stress is likely to play a causative role in the tissue and cellular damage in these diseases.[9,23] In particular, diabetes mellitus is strongly associated with increased oxidative stress,[24–28] which could be a consequence of either increased production of free radicals,[26,29–33] or reduced antioxidant defenses (Fig. 6).[34–37]

There is considerable evidence to indicate that oxidative stress plays an important role in the etiology of diabetic complications.[28,38–41] Many of the biochemical pathways (e.g. protein glycation, polyol pathway, glucose autoxidation) associated with hyperglycemia can result in increased free radical production (Fig. 7). Oxidative stress is not only associated with complications of diabetes, but has been also linked to insulin resistance.[42–44] *In vitro*, oxidative stress causes insulin resistance at multiple levels (*vide infra*).

An additional potential target of oxidative stress is likely to be the β-cell. While the process of glucose-stimulated insulin secretion is complex and is dependent upon many factors, the critical importance of mitochondrial metabo-

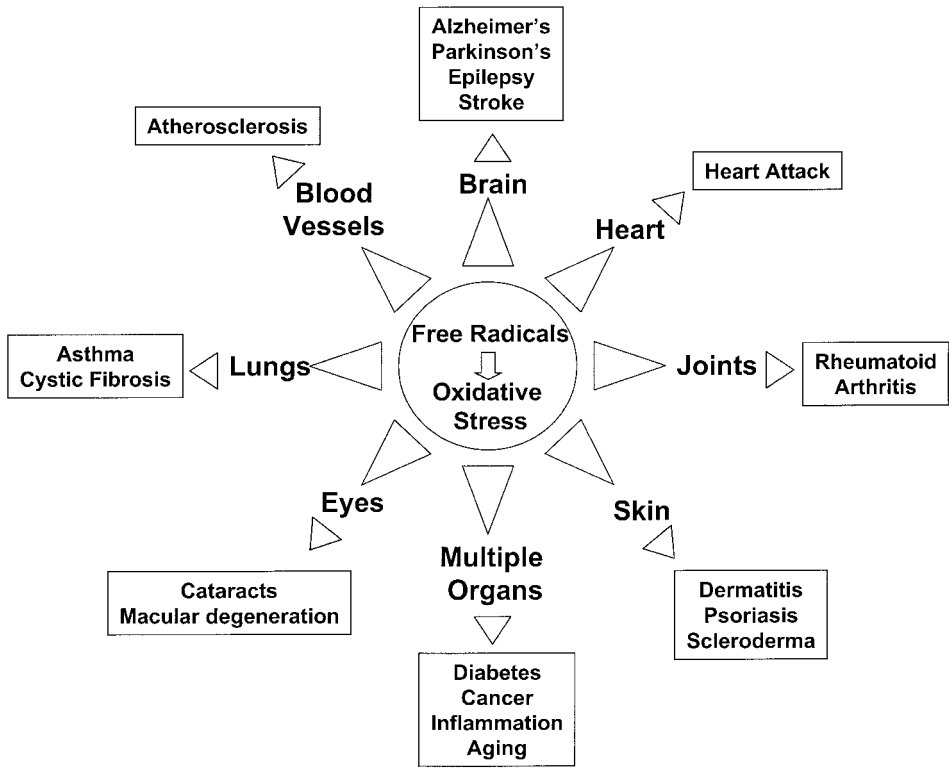

FIG. 5. Association of free radicals, oxidative stress, and disease. The generation of free radicals including reactive oxygen and nitrogen species leads to increased oxidative stress. As portrayed in the diagram, this process is not tissue-specific, and could be a consequence of either increased production of free radicals, or reduced antioxidant defenses. Although causality has not been equivocally demonstrated, there is a large body of experimental evidence that shows the association of increased levels of oxidative stress and a variety of pathological conditions.

lism in linking stimulus to secretion is well established.[45–48] As discussed earlier, mitochondria are free radical generators and their unwitting targets. Therefore, it is not surprising to learn that oxidative stress (e.g., H_2O_2) damages β-cell mitochondria and markedly blunts insulin secretion.[49] To make matters worse, β-cells are particularly susceptible to oxidative attack because of their inherently low level of antioxidant defenses.[50] Consistent with this proposal, there is growing evidence to show that antioxidants including DHLA, vitamins C and E, and *N*-acetyl-L-cysteine are able to exert a direct protective effect against free radical assault on insulin-secreting cells,[51–53] along with providing a benefit against the damages of glucose-mediated toxicity in rodents with diabetes.[52,53] In light of the negative physiological consequences commonly associated with increased oxidative stress, the idea of treating patients with type 2 diabetes pharmacologically with antioxidants to reduce oxidative stress is gaining increasing experimental support and clinical acceptance.[17,28,43,54–58]

α-LIPOIC ACID AND DIABETIC NEUROPATHY

LA was first used therapeutically in 1959 in Germany to successfully treat acute liver poisoning, and also has been used to treat other liver pathologies.[59,60] Shortly thereafter, LA was used to treat diabetes-induced neuropathy, despite the scarcity of information regarding the cause of this condition at that time. It was believed that LA increased glucose utilization in peripheral nerves. However, the report that LA levels are decreased in humans with diabetes and in some patients with polyneuritis and cardiovascular disease likely provided an additional rationale for administering LA to patients with diabetes, (i.e., replacement therapy.)[36] Berkson[61,62] was the first

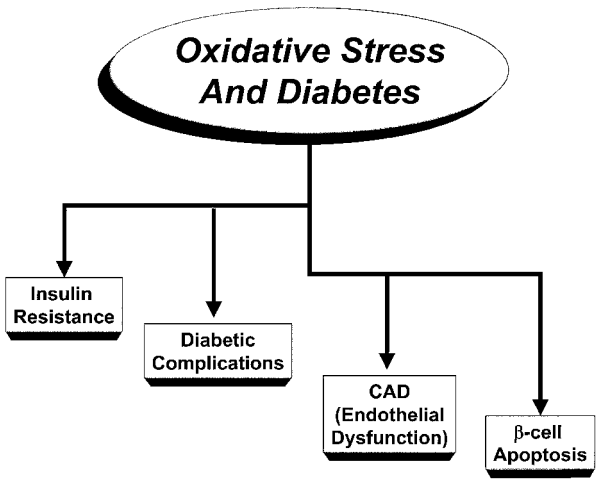

FIG. 6. Potential areas of impact of oxidative stress in diabetes and the pre-diabetic state. Free radical generation leading to oxidative stress has the capacity to impact diabetes at multiple levels. The role of oxidative stress leading to microvascular complications has the most experimental support. Oxidative stress also plays a significant role in the development of macrovascular complications, including promoting atherosclerosis and the inhibition of nitric oxide-mediated vasodilation.[21] More recent evidence suggests an association of oxidative stress with both impaired insulin action (*in vitro* and *in vivo*) and the deterioration of β-cell function.

to report the successful clinical use of LA in the United States, when he used it in 1977 to treat liver failure associated with mushroom poisoning following ingestion of *Amanita phalloides*.[61,62]

LA has been prescribed in Germany for over 30 years for the treatment of diabetes-induced neuropathy.[63–65] There have been four recent controlled clinical studies evaluating LA for the treatment of diabetes-induced neuropathy, and one study for the treatment of cardiovascular autonomic neuropathy. The overall conclusions are: (1) 3-week treatment with i.v. LA (600 mg) reduced the main symptoms of diabetes-induced polyneuropathy; (2) the effect is accompanied by an improvement in neuropathic deficits; (3) oral treatment with LA (800–1800 mg) for 4–7 months appears to improve neuropathic deficits and cardiac autonomic neuropathy; (4) preliminary data also suggest an improvement in motor and sensory function in lower limbs; (5) LA has an excellent safety profile at oral doses up to 1800 mg/day.

Taken together, these results suggest that i.v. administration of LA is efficacious, but that oral administration of LA is only marginally effective for the treatment of symptomatic features

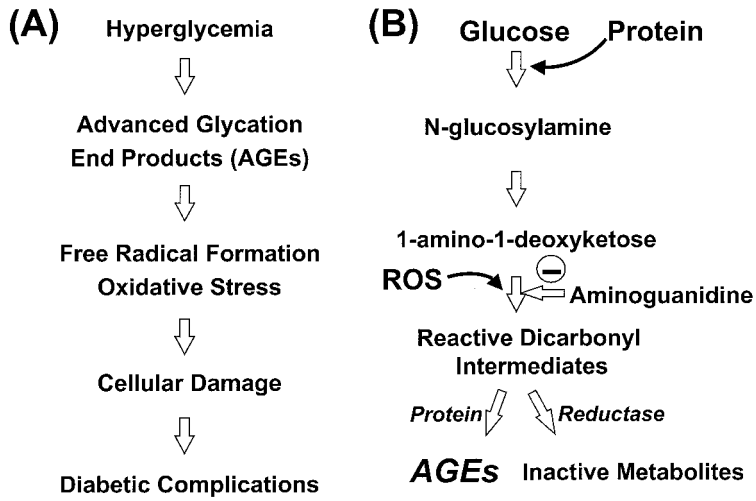

FIG. 7. Oxidative stress leads to complications of diabetes. **(A)** Chronic hyperglycemia can lead to diabetic microvascular disease by several possible routes.[38] Shown here is the route mediated by the formation of advanced glycation end products (AGEs). **(B)** AGEs form nonenzymatically from the oxidation of 1-amino-1-deoxyketose (Amadori product) mediated by reactive oxygen species (ROS), and also from metal-catalyzed auto-oxidation of sugars (not shown). Specific reductases can detoxify reactive dicarbonyl intermediates to inactive species. Aminoguanidine is a hydrazine compound that inhibits the formation of AGEs *in vivo* by reacting with the AGE precursor, 3-deoxyglucosone. AGEs can induce pathological changes by increasing oxidative stress, altering protein function, interfering with the normal extracellular matrix, and increasing soluble ligand production via interaction with cell-surface receptors.

of diabetes-induced neuropathy. A pivotal multicenter trail, **N**eurological **A**ssessment of **T**hioctic **A**cid in **N**europathy Study (NATHAN), is in process in Europe and North America to evaluate the ability of oral LA to slow the progression of diabetic neuropathy.[65] This study is using the most rigid statistical design and quantitative indices of efficacy of any trial performed to date. If efficacy is demonstrated, LA could become the first U.S. Food and Drug Administration (FDA)-approved treatment for diabetes-induced neuropathy.

BENEFITS OF α-LIPOIC ACID ON WHOLE-BODY GLUCOSE METABOLISM AND INSULIN SENSITIVITY IN TYPE 2 DIABETICS

There are several clinical studies that point to a beneficial effect of LA on whole-body glucose metabolism in patients with type 2 diabetes. In these studies, glucose metabolism and insulin sensitivity was assessed using the euglycemic-hyperinsulinemic clamp.[66,67] In 1995, Jacob et al.[68] were the first to report that acute intravenous infusion of 1000 mg of LA significantly improved insulin-stimulated metabolic clearance rate (MCR) and insulin sensitivity in patients with type 2 diabetes. Study subjects ($n = 13$) were well controlled by diet alone, or diet combined with glibenclamide. After LA treatment, the glucose infusion rate increased 47% ($p < 0.05$), MCR increased 55% ($p < 0.05$), and insulin sensitivity increased 57% ($p < 0.05$). No improvement was seen in the saline-treated control group.

Subsequently, the same group reported that repeated parenteral administration of 500 mg LA (daily infusions for 10 days) enhanced insulin-stimulated glucose disposal.[69] Study subjects ($n = 20$) were well controlled by diet alone, or diet combined with glibenclamide and/or acarbose. After treatment with LA for 10 days, MCR and insulin sensitivity were significantly increased by approximately 30% ($p < 0.05$).

To place these results in context, if the reported increases in MCR and insulin sensitivity were to persist with continued LA therapy, they would compare favorably with metformin (Glucophage™, Bristol-Myers Squibb, Princeton, NJ), a widely prescribed medication that increases insulin sensitivity and glucose utilization. For example, in patients with type 2 diabetes, a daily dose of 2 g metformin (monotherapy) for 3 months produced an approximate 25% increase ($p < 0.03$) in peripheral glucose disposal as measured by the euglycemic-hyperinsulinemic clamp.[70] Rosiglitazone (Avandia™, SmithKline Beecham, Philadelphia, PA), recently approved for use in patients with type 2 diabetes, is the most potent member of the thiazolidinedione class of insulin-sensitizing agents (compared with troglitazone or pioglitazone). Although we are unaware of any published data regarding the effect of rosiglitazone (or Actos™, Takeda Pharmaceuticals, Lincolnshire, IL and Eli Lilly, Indianapolis, IN; pioglitazone) monotherapay on insulin sensitivity and glucose utilization in patients with type 2 diabetes, addition of rosiglitazone (4 and 8 mg/day) to a maximum metformin regimen (2.5 g/day) further improved insulin sensitivity as measured indirectly using the homeostasis model assessment (HOMA; values increased by 1.7 units at 4 mg and 3.8 units at 8 mg).[67,71] Acarbose, an α-glucosidase inhibitor, has also been evaluated for its effect on insulin sensitivity in patients with type 2 diabetes and impaired glucose tolerance, and has yielded conflicting results.[72–75] It appears that although acarbose does not result in a decrease in insulin resistance, insulin sensitivity probably improves in the long-term as a result of improved metabolic control. Acarbose is currently being evaluated in an international study for its ability to prevent or delay the progression of impaired glucose tolerance to type 2 diabetes.[76]

The availability of enteric-coated tablets has permitted the evaluation of oral administration of LA to improve insulin-stimulated glucose disposal. In a randomized, placebo-controlled, multicenter study, LA (600, 1200, or 1800 mg per day) was administered to 74 patients with type 2 diabetes for 4 weeks.[77] Similar to the previous studies, subjects were well controlled by diet alone, or diet combined with other antihyperglycemic medications. Subjects in each arm of the study had a similar degree of hyperglycemia and insulin sensitivity at baseline. Compared with the placebo group, a greater percentage of patients who received LA treat-

ment exhibited an increase in MCR and insulin sensitivity. No differences were observed among groups receiving the different doses of LA. Thus, patients from each arm were combined into a single group for comparison with those who received a placebo. Overall, insulin sensitivity improved approximately 17% following LA treatment ($p < 0.05$). Fasting plasma glucose did not change, but there was a trend toward reduced fasting insulin.

Another recent open-label study evaluated orally administered LA on insulin sensitivity along with serum lactate and pyruvate levels in patients with type 2 diabetes. LA (1200 mg per day) was administered to 10 lean and 10 obese patients for 4 weeks.[78] Insulin sensitivity was assessed before and after treatment using the Bergman minimal model.[67,79] Following treatment with LA, lactate and pyruvate were reduced by approximately 45% after oral glucose loading ($p < 0.05$). In lean and obese patients with diabetes, LA increased insulin sensitivity by approximately 18–20%, although this effect was statistically significant only in the lean patients with diabetes ($p < 0.05$).

Results of published clinical studies showing the effects of LA on MCR are summarized in Figure 8. It is clear that i.v. administration of LA provides a metabolic benefit in type 2 diabetics by increasing insulin-stimulated glucose disposal (MCR). In the acute and chronic protocols, i.v. LA also markedly increased insulin sensitivity. In contrast to i.v. LA administration, the improvement in insulin sensitivity following oral administration of LA is only minimal, ~20%. This is evident despite the higher doses used (up to 1800 mg), and the longer treatment time (30 days oral vs.10 days I.V.).[77] Although the improvement in insulin sensitivity following oral administration of LA reached statistical significance in both studies, the magnitude of metabolic improvement bordered on the limit of sensitivity of the methods used for quantitation (i.e. euglycemic clamp and minimal model).[66,80]

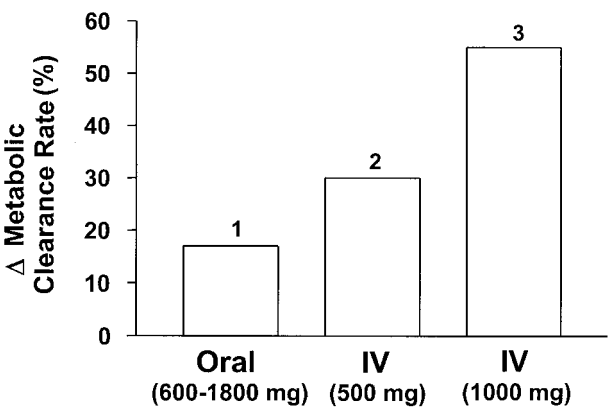

FIG. 8. Effects of α-lipoic acid on insulin-stimulated glucose metabolism in patients with type 2 diabetes. Intravenous (i.v.) administration of α-lipoic acid is able to significantly increase insulin sensitivity (as judged by % change [Δ] in metabolic clearance rate [MCR]) in patients with type 2 diabetes, while oral administration exerts a minimal effect (see text for details). (1) Seventeen percent increase in MCR ($p < 0.05$); data replotted from,[77] (2) 30% increase in MCR ($p < 0.05$); data replotted from,[69] (3) 55% increase in MCR ($p < 0.05$); data replotted from.[68]

LIMITED EFFICACY OF CURRENT ORAL FORM OF α-LIPOIC ACID DUE TO PHARMACOKINETIC PROFILE

A possible explanation for the marginal efficacy of oral LA therapy on insulin sensitivity might be provided by the abbreviated time therapeutic plasma levels of LA are maintained when taken orally. It is possible that this also might account for the lack of efficacy of oral LA therapy with regard to glycemic control. This plasma profile is a function of the short half-life of LA, along with its extensive presystemic elimination. Human pharmacokinetic studies have found that LA possesses an extremely short plasma half-life of about 30 minutes after both oral and i.v. administration.[81,82] Oral LA is rapidly absorbed: the maximum plasma concentration is reached within 30 minutes to 1 hour for doses up to 600 mg.[81–83] The absolute bioavailability after a single oral dose of 200 mg is approximately 30%. Furthermore, even after repeated oral administration of LA, it appears that accumulation in plasma is not achieved.[84,85] Presumably, this reflects the short plasma half-life and extensive presystemic elimination, which is thought to be primarily hepatic.[81] Thus, following oral LA administration, a maximum plasma level is quickly reached, but falls just as quickly to a level insufficient to impact insulin sensitivity or glucose control.

It is interesting to speculate that the superior ability of i.v. LA to improve insulin sensitivity might be due to the fact that i.v. administration

achieves a higher plasma level of LA, and maintains it for a longer duration.[81,82] In this context, the question is raised as to whether maintaining a therapeutically effective level of LA in plasma for an appropriate length of time (i.e., mimicking the i.v. LA situation) using controlled release drug delivery technology would increase insulin sensitivity and eventually result in a beneficial impact on glucose control in type 2 diabetics.

BENEFITS OF α-LIPOIC ACID ON GLUCOSE METABOLISM AND INSULIN ACTION IN CELLS

LA was first reported to enhance glucose utilization in isolated rat diaphragm 30 years ago.[86] Although the stimulatory effect of LA was rather small (~35%), it was evident in the absence of insulin, and partially additive with insulin. In contrast to the rapid onset of action of insulin, the effect of LA required a 2-hour treatment. The authors suggested that the stimulatory effect might be attributed to the presence of the sulfhydryl groups of LA. In a study published that same year, it was shown that thiols possessed insulin-like effects that were related to their content of sulfhydryl groups.[87]

More recently, a direct stimulatory effect of LA on glucose transport in cultured rat L6 myocytes and murine 3T3-L1 adipocytes was reported.[88] The effect was blocked by wortmannin, an inhibitor of phosphatidylinositol 3-kinase (PI 3-kinase), but partially additive with insulin, suggesting that LA was utilizing some but not all of the insulin signaling pathway. However, in this study as in the earlier one, the concentrations of LA required to achieve stimulation of glucose transport were high (2.5 mM), and unlikely to be achieved therapeutically. Following oral dosing of LA (600 mg), the plasma concentration of LA is typically in the range of 10–25 μM.[83*] (Evans JL and Goldfine ID. Manuscript in preparation.) Additional work from this group has shown that LA stimulates the plasma membrane-targeted translocation of GLUT1 and GLUT4, increases tyrosine phosphorylation of the insulin receptor and IRS-1, and increases PI 3-kinase and protein kinase B (PKB) activities.[89] These results provide further confirmation that high concentrations of LA are able to activate the insulin-signaling pathway leading to increased glucose transport and utilization. Similarly, a direct stimulatory, wortmannin-sensitive effect of LA on glucose transport in response to a millimolar concentration was recently reported in isolated cardiac myocytes.[90] However, the relationship and significance of the direct effect on glucose transport in cells exerted by millimolar concentrations of LA to its therapeutic effects in patients remains to be defined.

Results from recent experiments have uncovered an additional beneficial effect of LA on glucose metabolism. Importantly, this effect of LA is achieved at a potency that is consistent with its therapeutic plasma concentration. At the cellular level, agents that induce oxidative stress (e.g., H_2O_2) impair insulin action. In 3T3-L1 adipocytes and L6 muscle cells, treatment with H_2O_2 impairs insulin-stimulated glucose transport, GLUT4 translocation, and glycogen synthesis.[91–93] The inhibitory effects of H_2O_2 target the proximal steps in the insulin signaling cascade, including the suppression of insulin-stimulated insulin receptor and IRS-1 tyrosine phosphorylation.[94,95] Thus, oxidative stress renders cells insulin resistant.

In 3T3-L1 adipocytes and L6 muscle cells, LA is able to provide substantial protection against the damages of oxidative stress mediated by acute H_2O_2 exposure.[96*] (Evans JL and Goldfine ID, Manuscript submitted.) In each cell type, LA had only small effects on glucose utilization in cells that were not subjected to oxidative stress. When L6 muscle cells were exposed to oxidative stress using a H_2O_2 generating system (glucose and glucose oxidase), insulin stimulation of glucose transport was nearly abolished. Pretreatment with LA for 18 hours prevented this loss of insulin action. The beneficial effect of LA was detected at a concentration of 10 μM, and a maximal effect observed at 300 μM. (Evans JL and Goldfine ID, Manuscript submitted.) Interestingly, this concentration range corresponds to that which is effective at increasing *de novo* synthesis of glutathione in cells.[7] In 3T3-L1 adipocytes, LA protected against the H_2O_2-induced loss of insulin stimulated glucose uptake, GLUT4 translocation, and PKB activation.[96] Because therapeu-

tic concentrations of LA fall within this micromolar range,[68,69,83] it is possible that this protective effect of LA on insulin action *in vitro* is linked to its therapeutic effect *in vivo*.

It is not known with certainty how LA protects against oxidative stress-induced insulin resistance. It might reflect the ability of LA to maintain the intracellular redox balance either directly, or through increasing glutathione levels.[7,97] In this manner, the target tissues of LA including insulin-sensitive tissues would be protected, and presumably less susceptible to the consequences of stress-induced activation of serine kinase activity.[93,98–100] Increased phosphorylation of insulin receptor substrates on discrete serine or threonine sites decreases the extent of their tyrosine phosphorylation, and is consistent with impaired insulin action.[101–107] In conjunction with this possibility, maintaining the intracellular redox balance might also serve to block the stress-induced oxidation and inactivation of protein tyrosine phosphatases (PTPases).[108–110] It has been known for quite some time that phosphotyrosyl turnover is essential for insulin stimulated glucose transport in adipocytes and muscle.[111,112] Although the selective inhibition of certain PTPases such as PTP-1B improves insulin action,[113] nonselective oxidation of the cysteine residues required for catalytic activity inactivates PTPases and likely results in insulin resistance. A summary of this proposed mode of action is provided in Figure 9.

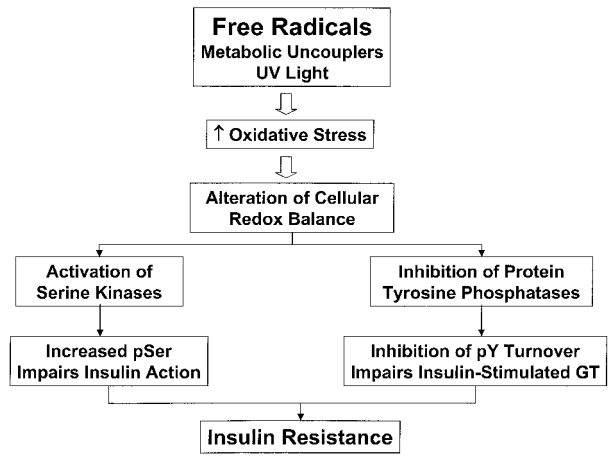

FIG. 9. Possible mode of action to account for the protective effects of α-lipoic acid against oxidative stress-induced insulin resistance. A variety of stimuli, including free radicals, oxidizing agents, inhibitors of oxidative phosphorylation, ultraviolet light (UV), and others increase cellular stress leading to the activation of serine/threonine kinase signaling cascades. Increased phosphorylation of insulin receptor substrates on discrete serine or threonine sites (pSer) decreases the extent of their tyrosine phosphorylation, and impairs insulin action.[102–107] In addition, oxidation of the cysteine residue in the catalytic site of protein tyrosine phosphatases by oxidixing agents, such as H_2O_2, can result in enzyme inactivation, interruption of phosphotyrosine (pY) turnover, and inhibition insulin-stimulated glucose transport (GT). The protective effects of α-lipoic acid (LA) and dihydrolipoic acid (DHLA) on oxidative stress-induced insulin resistance may be related to their ability to preserve the intracellular redox balance, acting either directly or through other antioxidants such as glutathione (GSH).

CONCLUSIONS AND IMPLICATIONS FOR DIABETES THERAPEUTICS

In its natural role, LA is a key component of several mitochondrial enzyme complexes responsible for oxidative glucose metabolism and cellular energy production. When used pharmacologically, LA and DHLA function as unique and effective antioxidants, recycling vitamins C and E and elevating glutathione levels. It is likely that increased cellular glutathione levels maintain intracellular redox balance, thereby offering a protective effective against free radical attack. Consequently, this provides a formidable barrier to the deleterious effects of stress-induced modulation of cellular signaling enzymes, alteration of gene expression, and ultimately might facilitate the preservation of mitochondrial function.

Clinical studies show that i.v. administration of LA is able to significantly increase insulin sensitivity in patients with type 2 diabetes, while oral administration of LA exerts a marginal effect. Furthermore, in clinical studies evaluating LA for the treatment of diabetes-induced neuropathy, i.v. administration of LA appeared to be more efficacious than oral administration. This limitation of oral therapy is a likely a function of the abbreviated duration for which a therapeutic level of LA is maintained in plasma. If the limitations of oral therapy can be overcome, then LA could emerge as a safe and effective adjunctive antidiabetic agent with insulin-sensitizing activity.

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