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The Potential Role of \( \alpha \)-Lipoic Acid in the Management of Diabetes Mellitus. Possible Molecular Mechanism

Abstract

\( \alpha \)-lipoic acid (LA) is synthesized in the liver and other tissues. In its physiological role, it acts as a co-factor in a multi-enzyme dehydrogenase complex, which generates acetyl-CoA and succinyl-CoA from pyruvate and \( \alpha \)-ketoglutarate respectively. Acetyl-CoA and succinyl-CoA are two important compounds participating in the Krebs cycle present in mitochondria. Thus, LA is an essential compound in the generation of ATP in mitochondria. Hyperglycemia in diabetes mellitus (DM) can result in the generation of reactive oxygen species (ROS) by way of a process called glycoxidation. ROS can damage important cell components such as membrane lipids, proteins and DNA. This cell damaging action of ROS has been implicated in the development of diabetic complications such as macro-angiopathy (atherosclerosis), micro-angiopathy (retinopathy, nephropathy), neuropathy and cataract. ROS can also damage \( \beta \)-pancreatic cells resulting in a decrease in insulin secretion. There is also evidence that ROS can cause insulin resistance, although its exact molecular mechanism remains to be elucidated. LA and its reduced form: dihydrolipoic acid (DHLA) do not appear to be present in the unbound state under normal conditions but are bound as lipoamide and dihydrolipoamide to a lysine residue present in dihydrolipoyl-transacetylase, one of the 3 subunits forming the multienzyme dehydrogenase complex. However, after dietary supplementation, both forms appear in various tissues in unbound forms. Exogenous LA is enzymatically reduced to DHLA. This latter compound is a strong anti-oxidant capable of scavenging ROS and regenerating endogenous anti-oxidants such as vitamin C, vitamin E and glutathione. LA has also been shown to bind Fe \( 2+ \), a transition metal ion required for the generation of hydroxyl radical (\( \cdot \)OH) the most active ROS. Thus the main potential role of LA in the management of DM is to prevent the detrimental effect of ROS generated by glycoxidation including the prevention or alleviation of glucose resistance. In the case of diabetic neuropathy, other potential roles include the enhancement of ATP production since glucose uptake in neurons is not insulin dependent, and possibly also increased synthesis of the neurotransmitter acetylcholine due to the increased availability of acetyl-CoA.

Keyword : \( \alpha \)-lipoic, acid, diabetes, mellitus, reactive, oxygen, species, (ROS), diabetic, complication,

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