

The pharmacology of the antioxidant lipoic acid.

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Abstract

1. Lipoic acid is an example of an existing drug whose therapeutic effect has been related to its antioxidant activity. 2. Antioxidant activity is a relative concept: it depends on the kind of oxidative stress and the kind of oxidizable substrate (e.g., DNA, lipid, protein). 3. In vitro, the final antioxidant activity of lipoic acid is determined by its concentration and by its antioxidant properties. Four antioxidant properties of lipoic acid have been studied: its metal chelating capacity, its ability to scavenge reactive oxygen species (ROS), its ability to regenerate endogenous antioxidants and its ability to repair oxidative damage. 4. Dihydrolipoic acid (DHHLA), formed by reduction of lipoic acid, has more antioxidant properties than does lipoic acid. Both DHHLA and lipoic acid have metal-chelating capacity and scavenge ROS, whereas only DHHLA is able to regenerate endogenous antioxidants and to repair oxidative damage. 5. As a metal chelator, lipoic acid was shown to provide antioxidant activity by chelating Fe²⁺ and Cu²⁺; DHHLA can do so by chelating Cd²⁺. 6. As scavengers of ROS, lipoic acid and DHHLA display antioxidant activity in most experiments, whereas, in particular cases, pro-oxidant activity has been observed. However, lipoic acid can act as an antioxidant against the pro-oxidant activity produced by DHHLA. 7. DHHLA has the capacity to regenerate the endogenous antioxidants vitamin E, vitamin C and glutathione. 8. DHHLA can provide peptide methionine sulfoxide reductase with reducing equivalents. This enhances the repair of oxidatively damaged proteins such as alpha-1 antiprotease. 9. Through the lipoamide dehydrogenase-dependent reduction of lipoic acid, the cell can draw on its NADH pool for antioxidant activity additionally to its NADPH pool, which is usually consumed during oxidative stress. 10. Within drug-related antioxidant pharmacology, lipoic acid is a model compound that enhances understanding of the mode of action of antioxidants in drug therapy.

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