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Letter to the Editors

The Mechanism of Action of Zinc-histidine Complex (Curazink®) As An Antioxidant

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Zinc-histidine (Curazink®, Redinomedica AG, Munich, Germany), a metal organic compound, is increasingly used as a supplement to treat zinc deficiency due to its efficient bioavailability.[1] Zinc has been proposed to have antioxidant properties both *in vitro* and *in vivo*. For example, it has been suggested that zinc may in part be antiatherogenic by inhibiting oxidative stress-responsive events involved in endothelial cell dysfunction.[2] In addition, amino acids, such as histidine, can also function as antioxidants in protecting LDL against copper-induced lipid peroxidation through the chelation of the transition metal ions.[3] Thus, we were interested in the ability of a combined zinc-histidine complex to function as an antioxidant in scavenging peroxyl radicals and chelating copper, relative to that of zinc sulphate.

Zinc-histidine is able to protect human LDL from copper-induced oxidation as measured by its concentration-dependent effects on the formation of conjugated dienes. Expressing the lag phase for the copper-induced oxidation of LDL as 100%, increasing the concentration of zinc-histidine complex from 2.5 to 10 mM enhances the lag phase to oxidation from 124% at 2.5 mM concentration to 295% at 10 mM, almost a factor of 3 above that in the absence of the compound. However, zinc sulphate was ineffective, consistent with a human volunteer study demonstrating that ingestion of 220 mg/day had no effect on the oxidizability of LDL *ex vivo*.[4] This identifies histidine as the active component in the zinc-histidine complex. The potency of zinc-histidine to inhibit LDL oxidation was lower than that of the comparable amount of histidine (1 mol zinc histidine, which contains 2 molecules of histidine, compared with 2 mol histidine).

In the course of inflammatory diseases, plasma histidine levels appear decreased, whereas supplementation of histidine leads to increased plasma levels.[5–8] This is supported by the finding that levels of histidine in plasma vary depending on the disease state and pharmacotherapy.[5–8] In addition, there seems to be a preferential complexing of zinc and copper with histidine in human plasma.[9] The formation of complexes with copper and zinc by histidine may represent a specific transport mechanism for these both trace elements in the human plasma.[10] *In vitro* studies of Hinsbergh *et al.*[11] demonstrated that histidine can prevent LDL modification, because it could act as a singlet oxygen scavenger, but could also complex Cu^{2+} ions and thus prevent lipid peroxidation. Plasma enriched in zinc-histidine may thus protect LDL from oxidation in the circulation. Histidine is a copper-chelator[10,11] at a concentration (25 μM) well below its plasma level, which is about 90 μM, and at physiological concentrations strongly inhibits lipid peroxidation.[3]

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Histidine is also an effective chelator of zinc, and clinical studies in human subjects have shown a positive effect of histidine on zinc absorption as measured by the increase in plasma zinc.[12] The bioavailability of zinc could be increased by application of zinc-histidine complexes as zinc sources compared to zinc sulphate as a zinc source. Histidine may enhance tissue uptake of zinc in man; a 15 mg dose of zinc as zinc-histidine complex seems to be equivalent to a 45 mg dose as zinc sulphate.[1]

The *in vitro* results reported here show that zinc-histidine, in addition to its ability to improve zinc absorption, could also contribute to the antioxidant status of plasma, providing antioxidant properties against LDL oxidation (as well as other pathophysiological processes) through transition metal-chelating mechanisms. Zinc-histidine had a strong concentration-dependent inhibitory effect on LDL oxidation, while zinc sulphate was ineffective in protecting LDL. Therefore, the advantage of the zinc-histidine complex over zinc sulphate is clear. It should be noted that the release of copper ions in atherosclerotic lesions has been reported as a later event in atherosclerosis.[13] Thus the ready uptake of zinc-histidine complex into the circulation may provide a way of contributing to the inhibition of such potentially deleterious oxidative processes mediated by copper ions.

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