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Metals, toxicity and oxidative stress.

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Abstract

Metal-induced toxicity and carcinogenicity, with an emphasis on the generation and role of reactive oxygen and nitrogen species, is reviewed. Metal-mediated formation of free radicals causes various modifications to DNA bases, enhanced lipid peroxidation, and altered calcium and sulfhydryl homeostasis. Lipid peroxides, formed by the attack of radicals on polyunsaturated fatty acid residues of phospholipids, can further react with redox metals finally producing mutagenic and carcinogenic malondialdehyde, 4-hydroxynonenal and other exocyclic DNA adducts (etheno and/or propano adducts). Whilst iron (Fe), copper (Cu), chromium (Cr), vanadium (V) and cobalt (Co) undergo redox-cycling reactions, for a second group of metals, mercury (Hg), cadmium (Cd) and nickel (Ni), the primary route for their toxicity is depletion of glutathione and bonding to sulfhydryl groups of proteins. Arsenic (As) is thought to bind directly to critical thiols, however, other mechanisms, involving formation of hydrogen peroxide under physiological conditions, have been proposed. The unifying factor in determining toxicity and carcinogenicity for all these metals is the generation of reactive oxygen and nitrogen species. Common mechanisms involving the Fenton reaction, generation of the superoxide radical and the hydroxyl radical appear to be involved for iron, copper, chromium, vanadium and cobalt primarily associated with mitochondria, microsomes and peroxisomes. However, a recent discovery that the upper limit of "free pools" of copper is far less than a single atom per cell casts serious doubt on the in vivo role of copper in Fenton-like generation of free radicals. Nitric oxide (NO) seems to be involved in arsenite-induced DNA damage and pyrimidine excision inhibition. Various studies have confirmed that metals activate signalling pathways and the carcinogenic effect of metals has been related to activation of mainly redox-sensitive transcription factors, involving NF-kappaB, AP-1 and p53. Antioxidants (both enzymatic and non-enzymatic) provide protection against deleterious metal-mediated free radical attacks. Vitamin E and melatonin can prevent the majority of metal-mediated (iron, copper, cadmium) damage both in vitro systems and in metal-loaded animals. Toxicity studies involving chromium have shown that the protective effect of vitamin E against lipid peroxidation may be associated rather with the level of non-enzymatic antioxidants than the activity of enzymatic antioxidants. However, a very recent epidemiological study has shown that a daily intake of vitamin E of more than 400 IU increases the risk of death and should be avoided. While previous studies have proposed a deleterious pro-oxidant effect of vitamin C (ascorbate) in the presence of iron (or copper), recent results have shown that even in the presence of redox-active iron (or copper) and hydrogen peroxide, ascorbate acts as an antioxidant that prevents lipid peroxidation and does not promote protein oxidation in humans in vitro. Experimental results have also shown a link between vanadium and oxidative stress in the etiology of diabetes. The impact of zinc (Zn) on the

immune system, the ability of zinc to act as an antioxidant in order to reduce oxidative stress and the neuroprotective and neurodegenerative role of zinc (and copper) in the etiology of Alzheimer's disease is also discussed. This review summarizes recent findings in the metal-induced formation of free radicals and the role of oxidative stress in the carcinogenicity and toxicity of metals.

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