Satellite Minisymposium: Metal Ions – Health and Food

Z1

Changes of Biological Significance Induced by Metal Ions in the Structure of Nucleic Acids and Nucleotides

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We have previously shown that the action of metal ions on nucleic acids leads to a variety of perturbations in secondary structure, including crosslinking, mispairing, and degradation. We have demonstrated that metal ions also have a profound effect on the way in which nucleic acid molecules are packed together into highly organized aggregates [1]. These studies, along with those that reveal that metals also influence the enzymes that act on nucleic acids (such as cleavage enzymes and RNA polymerase) indicate how changes in cellular concentrations of metal ions can impact on cellular processes that depend on genetic information transfer.

Many of the effects of metals on nucleic acids or other biomacromolecules involve conformational changes. We have recently been concerned with the ability of metal ions or complexes to induce interconversions among at least four nucleic acid conformers [2]. These studies were carried out with poly(dGdC)·poly(dGdC), which can exist in the Z-conformation, and we have discovered that conversion to Z-DNA can lead to further conversions to other DNA structures. These structures are all in equilibrium with each other, but each can be stabilized under appropriate conditions of nucleic acid and metal concentration. These conformational transitions are important because the biological activity of nucleic acids depends on their conformation. We have shown that different conformations of DNA have different activities as template for RNA synthesis.

It has been reported that the progress of Alzheimer's disease, the most prevalent form of senile dementia, is associated with the accumulation of aluminum in the chromatin of the brain [3, 4]. We have found that Al forms crosslinks between DNA strands and that Al binding to DNA in chromatin can be monitored by nuclear magnetic resonance (NMR). Al has also been implicated in dialysis dementia [5] through binding to ATP [6]. We have found by multinuclear NMR studies that Al forms four different complexes [7] with ATP. ^{27}Al NMR is very sensitive to the chemical environment of Al and can be used in the identification of Al complexes in equilibrium with each other in a variety of systems of biological interest [8].

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Z2

Nickel Carcinogenesis

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Increased incidences of cancers of the lung, nasal sinus, larynx, and possibly kidney have occurred among workers in nickel refineries: the identity of the nickel compounds that produce cancers in nickel workers remains uncertain, although principal attention is focused on (a) insoluble dusts of nickel subsulfide (Ni_3S_2) and nickel oxide (NiO), (b) the vapor of nickel carbonyl ($Ni(CO)_4$), and (c) soluble aerosols of nickel sulfate ($NiSO_4$) or nickel chloride ($NiCl_2$). Cancers have been induced in experimental animals by several nickel compounds by a variety of routes, including (a) lung cancers by inhalation of $Ni(CO)_4$ and Ni_3S_2 in rats, (b) sinus cancers by implantation of Ni_3S_2 in cats, (c) renal cancers by implantation of Ni_3S_2 in rats, and (d) sarcomas by im injection of Ni_3S_2 in mice, rats, hamsters, and rabbits. In the author's laboratory, 18 nickel compounds have been tested for carcinogenicity in male Fischer rats by a single im injection at equivalent dosages (14 mg Ni/rat). Within two years, the following incidences of sarcomas developed at the injection site: Ni_3S_2, 100%; crystalline NiS, 100%; Ni_4FeS_4, 100%; NiO,

93%; Ni_3Se_2, 91%; NiAsS, 88%; NiS_2, 86%; Ni_5As_2, 85%; Ni dust, 65%; NiSb, 59%; NiTe, 54%; NiSe, 50%; $Ni_{11}As_8$, 50%; amorphous NiS, 12%; $NiCrO_4$, 6%; NiAs, 0%; NiFe alloy, 0%; $NiTiO_3$, 0%, vehicle controls (N = 84), 0%. Distant metastases were found in 109 of 180 sarcoma-bearing rats (61%). The histological classification of the nickel-induced sarcomas included rhabdomyosarcoma, 52%, fibrosarcoma, 18%, undifferentiated sarcoma, 13%, osteosarcoma, 8%, and miscellaneous sarcomas, 9%. Relative carcinogenic activities of the compounds were not significantly correlated with dissolution half-times in rat serum or phagocytic indices by rat peritoneal macrophages *in vitro*. The relative carcinogenic activities were correlated ($P < 0.001$) with potencies of the compounds to stimulate erythropoiesis in rats after intrarenal injection. The mechanism of nickel carcinogenesis may involve binding of nickel to nucleoproteins, with inhibition of nucleic acid synthesis, formation of DNA–protein cross-links, impaired fidelity of DNA replication, and induction of chromosomal aberrations, including sister–chromatid exchanges and karyotypic anomalies. Manganese antagonism of nickel carcinogenesis may indicate competition of Mn(II) and Ni(II) for binding to specific loci on nucleoproteins or DNA polymerases.

Z3

Nutritional Aspects of Zn Deficiency

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Zinc, which as been recognized as essential to man, has received considerable attention in recent years for its metabolic role. Zinc is an essential component of an number of enzyme systems and influences the structural configuration of certain nonenzyme organic ligands.

Several experimental studies have emphasized that many systems may be adversely affected by zinc deficiency, particularly if the deficiency occurs when cells of the particular system are rapidly dividing, growing, or synthesizing proteins.

Features of nutritional zinc deficiency in animals and men include anorexia, growth retardation, impaired keratogenesis, skin lesions, hypogonadism, hypogeusia, lethargy and behavioral changes.

Zinc-responsive growth failure and delayed sexual maturation were described in adolescent males from the Middle East. Furthermore, zinc deficiency has been reported in people maintained on long-term parenteral nutrition or suffering from alcoholism, chronic renal disease or malabsorption syndromes.

Recognition of the critical role of zinc in human nutrition has recently led to the hypothesis that in elderly persons, some degenerative changes result with advancing years from insufficient intake of protein foods that are the best dietary sources of this metal ion.

Z4

The Role of Aluminum in Experimental Osteomalacia. Preliminary Results: Aluminum Content and Bone Mineralization

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In order to clarify the role of aluminum in the production of dialysis osteomalacia, an experimental study on rats has been carried out. Four groups of fifteen rats each have been treated daily with intraperitoneal injections of aluminum chloride for periods of up to three and half months.

Acute, sub-acute and chronic intoxication have developed in the treated rats.

The aluminum presence in the bony tissue has been determined both quantitatively and morphologically by means of atomic absorption spectrophotometry and specific histochemical studies. In this way we have studied the preferential localization of the aluminum in the bony tissue with reference to the mineralization processes.

Z5

A Pharmacological Analysis of Aluminium Effects on the Central Nervous System

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The possible causes of dementia are many, and most cases are associated with degenerative disease of the central nervous system; therefore, analysis of neurotransmitter systems may provide valuable information on the selectivity of the degenerative process. This report will deal with an experimental approach