Metabolism of Trace Metals in Man

Volume II
Genetic Implications

Editors

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PREFACE

The importance of trace metals in human health and normal development is receiving more and more attention. As a consequence of advancement in analytical techniques and sophisticated instrumentation in the past two decades, there has been a rapid expansion in biomedical research on trace elements. An increasing number of trace elements have been found to be essential for life processes. Pronounced alterations in trace metal concentrations in tissues or body fluids have been frequently observed in response to certain clinical conditions such as infection, stress, malignant diseases, hormonal changes, etc. Changes in trace metabolism during development are gradually being investigated and identified. Teratogenic effects of specific deficiency or excesses of trace metal are becoming an increasing concern to developmental biologist and pediatricians. New human and animal mutants with abnormal metal metabolism have been reported in recent years. The study of trace metals no longer constitutes a small subdivision in nutrition. Its importance is significant to modern nutritionists, biochemists, molecular biologists, developmental biologists, geneticists, environmental scientists, pediatricians and other clinical disciplines.

A vast literature exists dealing with trace metals and a number of outstanding monographs deal with the biological, biochemical, or clinical effects of a specific trace metal or trace metals in general. However, newer aspects of trace metal research, i.e. the developmental aspects and genetic implications, have not been systematically discussed in any existing texts. The present two volumes will summarize the present status of research in these areas and serve as milestones for future development in these areas of trace metal research.

THE EDITORS

Owen M. Rennert, M.D., is Professor and Head of the Department of Pediatrics, Chief of the Section of Genetics, Endocrinology, and Metabolism, Professor, Department of Biochemistry and Molecular Biology, and Director of the Program in Human Genetics in the Departments of Biochemistry and Molecular Biology and Pediatrics at the University of Oklahoma Health Sciences Center, Oklahoma City. Dr. Rennert is also Chief of the Pediatric Service of the Oklahoma Children's Memorial Hospital, Oklahoma City.

Dr. Rennert received his M.S. (Biochemistry) and M.D. from the University of Chicago. He completed his internship and residency and a postdoctoral fellowship in biochemistry at the University of Chicago as well.

During his military service, from 1964 to 1966, Dr. Rennert was a Senior Surgeon with the U.S. Public Health Service and concurrently held the position of Research and Clinical Associate at the NINDB, NIH, Section of Pediatric Neurology of the Public Health Service, Bethesda, Maryland. Returning to the University of Chicago in 1966, Dr. Rennert worked as an Instructor and as Chief Resident (1966 to 1967) and as an Assistant Professor (1967 to 1968) in the Department of Pediatrics. From 1968 to 1977, Dr. Rennert was on the faculty of the University of Florida College of Medicine, Gainesville, in the Departments of Pediatrics, Biochemistry, and Neuroscience, and from 1970 to 1978 was Head of the Institutional Division of Genetics, Endocrinology, and Metabolism and Director of the Sunland Training Center. Dr. Rennert has been in his current position since 1977.

Dr. Rennert is active in numerous professional societies whose interests include clinical research, pediatrics, and biochemistry and has served as Chairman, Co-Chairman, and Recorder at conferences of the Cystic Fibrosis Foundation, the American Association of Clinical Scientists, the Society for Pediatric Research, the American Pediatric Society, and the Gordon Conference on Polyamines. He was Vice-President Elect of the American Association of Clinical Scientists in 1980, and is currently on the Editorial Boards of the *American Journal of Clinical Research* and *Annals of Clinical and Laboratory Science*.

Dr. Rennert has contributed to over 200 publications. His current research interests include growth and differentiation in humans, the role of trace metals in growth and differentiation, and the fundamental processes by which trace metals affect growth and differentiation in humans.

Wai-Yee Chan, Ph.D., is an Associate Professor in the Department of Pediatrics and the Department of Biochemistry and Molecular Biology at the University of Oklahoma Health Sciences Center, Oklahoma City. He is also Co-Scientific Director, Trace Metals Laboratory of the State of Oklahoma Teaching Hospitals, and a Consultant in Medical Service to the Veteran's Administration Medical Center, Oklahoma City.

Dr. Chan received his B.Sc. with First Class Honors in Chemistry from the Chinese University of Hong Kong. He received his Ph.D. in Biochemistry from the University of Florida, Gainesville and was a Postdoctoral Fellow in Biochemistry at the University of Oklahoma. Dr. Chan has been affiliated with the University of Oklahoma since 1977.

Dr. Chan is active in numerous professional societies whose interests include clinical research, nutrition, biochemistry, and pediatrics. He is a national committee member of the Council on Pediatrics and the Council on Trace Metals of the American College of Nutrition. In recent years, Dr. Chan has been invited to participate in conferences held by the Cystic Fibrosis Foundation, the NIH, Ross Laboratories, annd the Hospital for Sick Children, Toronto, and has served as the American Delegate to the First U.S.-China Bilateral Conference on Protein in Biology and Medicine and as Coordi-

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Dr. Chan has contributed to numerous publications in his field of interest and has presented papers to meetings of the American Society of Human Genetics, the Association of Clinical Scientists, the American Pediatric Society, NATO ASI, the Southern Society for Pediatric Research, and the American College of Nutrition. In addition, he has conducted seminars at the University of Florida, the Oklahoma Medical Research Foundation, the University of Oklahoma, the Shanghai Institute of Biochemistry of the Chinese Academy of Science, Shanghai, and the Institute of Basic Medical Science of the Chinese Academy of Medical Science, Beijing.

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Chapter 1

INTRODUCTION: METAL IONS AND GENETIC REGULATION

Gunther L. Eichhorn

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I. INTRODUCTION

Metal ions play a role in numerous biological and biochemical processes, and among these processes genetic regulation is of great importance. Metal ions are required for all aspects of genetic information transfer. These essential metal ions are acquired by biological organisms, including man, from the environment. These metal ions can sometimes accumulate in various tissues and organs in abnormal concentrations, and under such conditions lead to harmful effects. Metal ions with no known benefits and only potentially harmful consequence to the body can also accumulate in this way.

We shall briefly consider in this introduction some of the changes in the structure of nucleic acids brought about by metal ion interaction, some of the metal requirements for the synthesis of DNA, RNA, and protein and the deleterious effects of metals in these processes, and finally some of the consequences of these effects for disease and aging.

II. METAL IONS AND NUCLEIC ACID STRUCTURE

Since the nucleic acids are the primary carriers of genetic information, any substance that can affect the structure of these molecules has the potential for a significant impact on genetic regulation. Metal ions have some very dramatic effects on nucleic acid structure.

A. Conformational Modification

Metal ions can be very influential in determining the three-dimensional structure of nucleic acids. The absence of metal ions can destabilize the DNA double helix and lead to the formation of a randomly coiled structure.[1] Different metal ions can stabilize either double-helical, single-helical, or random coil forms of nucleic acids; these three forms, respectively, have been shown to be favored by sodium, Ni(II) and Cu(II) for polyadenylic acid, under otherwise similar conditions.[2]

The transitions between various forms of double-helical DNA have become of great interest recently with the discovery of the left-handed double helix, Z-DNA, that can occur when guanine and cytosine bases alternate in the DNA base sequence.[3] The Z structure is produced under conditions of high salt from B-DNA, the more commonly known right-handed DNA double helix.[3,4] Transitions to other double-helical DNA structures, such as the A form,[5] are also mediated by metal ions. Since the DNA structure is believed to be important in recognition processes, these transitions in structure may be of significance in genetic regulation.

It should be pointed out that the role of metals in these processes involves their positive charge, and that other positively charged substances, e.g., polypeptides and proteins, can take the place of metals in some of these transitions.

B. Crosslinking

Metal ions such as copper[6] and silver[7] can form crosslinks between DNA strands, and in this way become a part of the DNA structure and significantly transform it.

C. Association and Compaction

DNA molecules are capable of associating with each other so as to form highly ordered aggregates, some of which are called ψ-structures[8] and are characterized by highly intense circular dichroism (CD). This association of DNA molecules with other DNA molecules results in a highly compacted arrangement of the DNA, and is fostered under a variety of conditions, such as the presence of positively charged protein or polypeptide chains. Metal ions are instrumental in determining the degree to which the DNA molecules are ordered as well as whether the aggregates are twisted in a right- or left-handed direction.[9] For example, metal ions can transform a ψ-structure with a negative CD spectrum to one with a positive CD.[10]

D. Mispairing

The correct transmission of the genetic code during DNA, RNA, as well as protein synthesis depends on the hydrogen bonding between the complementary Watson-Crick base pairs. If hydrogen bonding does not occur exclusively between these complementary base pairs, errors can occur in genetic transmission. The metal ion concentration has been shown to be of importance in determining whether only Watson-Crick base pairs are formed or whether mispairing of bases occurs.[11] Such mispairing, which occurs at high concentrations of metal ions, could result in errors in information transfer.

E. Degradation

Under certain conditions metal ions can catalyze the degradation of RNA,[12,13] although this reaction occurs in vitro at a substantial rate only at elevated temperature. DNA is not subject to such degradation by metal ions alone, but in the presence of other substances, e.g., peroxide, metal ions can also take part in the disintegration of DNA.[14]

III. METAL IONS AND DNA, RNA, AND PROTEIN SYNTHESIS

All of the steps in the transfer of genetic information from DNA to cellular protein require the participation of metal ions. The structure of chromatin in the nucleus is very much dependent upon the metal ion concentration. It has been demonstrated by electron microscopy, for example, that chromatin particles in the cell nucleus appear compacted in the presence of a relatively high magnesium concentration, and highly dispersed when the magnesium concentration is lowered.[15] Changes in metal ion concentration can reverse either the compaction or the dispersion of the chromatin material. Since the chromatin structure is important in both DNA replication and transcription to RNA, these effects of metal ions could be significant for genetic regulation.

DNA and RNA synthesis are mediated by DNA and RNA polymerase enzymes, which contain zinc as an integral part of their structure.[16,17] There is evidence that these metals are important in the function of these enzymes.[16,17] In addition to the zinc that is intrinsic to the enzymes, the latter also require the presence of other divalent cations, i.e., Mg(II), Mn(II), or Co(II).[16] These metal ions seem to be as important as the zinc for the mechanism of DNA and RNA synthesis, and moreover, the nature of the activating metal ion is a vital factor in determining the fidelity of the synthetic processes.[18] Fidelity in terms of base pairing is three and five times as high in the presence of Mg(II) than in the presence of Mn(II) and Co(II), respectively.[18] Fidelity in terms of sugar incorporation is also affected by the activating metal. In the presence of Mg(II) very little ribonucleotide is incorporated into DNA or deoxynucleotide into RNA, but in the presence of Mn(II) these misincorporations are much more frequent.[19,20] Thus the presence of Mn(II) in DNA and RNA synthesis can lead to a variety of errors in replication and transcription.

Many of the complicated processes that culminate in the synthesis of proteins require metal ions. The structure of the ribosomes, on which protein synthesis occurs, is dependent on metal ion concentration.[21] The binding of transfer RNA to messenger RNA, the structures of the RNA molecules, and their binding to the ribosome,[22] are all mediated by metal ions. Nevertheless, excess metal ion can cause the incorporation of the wrong amino acid into protein.[23] Since a mistake in the recognition of a codon in messenger RNA by the anticodon in transfer RNA would lead to such misincorporation, the latter may result in part from the mispairing of codon and anticodon bases that would lead to the binding of the "wrong" transfer RNA molecule holding a "wrong" amino acid for placement into a site on the protein molecule.

Thus metal ions are required in all the steps that lead from the replication of DNA through its transcription into RNA and finally translation into protein, and at the same time the

"wrong" metal ion or the essential metal in the "wrong" concentration can lead to errors in each of these steps.

IV. SOME CONSEQUENCES OF METAL EFFECTS ON DISEASE AND AGING

The dramatic effects of metals on nucleic acid structure and genetic processes could be expected to have important consequences to living organisms. Metal ions that are essential for life must be incorporated from the environment, and therefore these metals as well as unessential metals can accumulate in excessive amounts.

A number of metal ions have been shown to be mutagenic and some of these are also carcinogenic.[24] Although the mode of action of the carcinogenic metals is not known, studies have been carried out on a mechanism by which the highly carcinogenic chromium introduced as Cr(VI) is reduced to Cr(III) that then binds to DNA.[25] Mutagenicity of metals has been correlated with relatively low fidelity in DNA synthesis.[26]

Metal binding to DNA has been successfully applied in the treatment of cancer. *Cis* $[Pt(NH_3)_2Cl_2]$ binds to DNA by attaching itself to two adjacent guanine groups[27,28] on the DNA molecule. This substance is the drug of choice for the treatment of a number of tumors.[29]

A variety of studies have shown that metal ions accumulate in cells as a function of age.[11] It may be that transport and excretory processes for metals are imperfect enough so that over long periods of time metal ion concentrations higher than those desired are attained. In view of the many potentially deleterious effects of metals on genetic information transfer that we have discussed, it is not unreasonable to expect that the increased metal ion concentrations could have an impact on this transfer and therefore on the aging process.[11] There is in fact some evidence that a rather specific process related to aging may be involved with metal accumulation. When brain autopsies of patients with Alzheimer's disease were analyzed for Al(III), increased localized concentrations of Al(III) were found, as compared to "normal" controls.[30] The Al(III) binds to the chromatin of the cell,[31] and has been found to crosslink DNA strands;[32] it has nevertheless not been demonstrated that Al(III) actually has any bearing on the progress of the disease.

V. CONCLUDING REMARKS

It is to be expected that metal ions are directly involved in the genetic regulation of metal metabolism; such regulation will be discussed in Chapter 2. This introduction serves to demonstrate some of the interactions of metal ions with the molecules of the genetic apparatus, and is intended to suggest how metal ions may be involved generally in genetic regulation. It should be pointed out, however, that many of the interactions that have been considered were studied in vitro, and often in isolated form. Much remains to be learned about the way in which metal ions take part in genetic regulation in vivo.

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Chapter 2

MOLECULAR AND SOMATIC CELL GENETICS ANALYSIS OF METAL METABOLISM IN CULTURED CELLS

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