

HEAVY METAL TOXICITY: IMPLICATION FOR CANCER AND ORTHOPAEDIC EFFECT



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TOXICOKINETICS

- **HEAVY METAL:** e.g Pb, Ar, Hg, Cd, Cr etc. are generally regarded as environmental chem.
- **SOURCE AND MODE OF ENTRY:**
- Air, agric products, marine products, industrial works,

HEAVY METALS AND BIOLOGICAL REACTIVE LIGANDS

- . **HEAVY METALS** = exert their toxic effects by combining with one or more reactive grps essential for normal physiological fnx.

E.G = -OH, -COO,

Sulfur grp: -SH, -S-S-

Nitrogen grp : NH_2 and NH (Klaasen 1996)

CANCER FORMATION

- Definition:
- **A disease cond. of uncontrolled cell proliferation and spread**
- **NEOPLASM= (new cell growth) interchanged with cancer**
- **BENIGN= neoplasm with localized growth**
- **MALIGNANT = neoplasm with characteristics of invasiveness and metastasis**

Characteristics of cancer cell

- UNCONTROLLED PROLIFERATION
- LOSS OF FUNCTION
- INVASIVENESS
- METASTASIS

CASINOGENS

- **DEFINITION: Agents or subst. that cause cancer**
- **E.g = Heavy metals**
- **= Asbestors**
- **= Benzen**
- **= Radon**
- **= Virus**
- **= etc (Chu and Santorelli 2012)**

CASINOGEN (mechanism of action)

- **Inactivation** of tumor suppressor gene in a cell
- **Activation** of proto- oncogens

ORTHOPAEDIC ANGLE (ARTHRITIS)

- **Seen generally as the dx of the joint and the surrounding tissues**
- **Symptoms include pain, joint stiffness and swelling mostly in the morning, aching**
- **Arthritis also affects other parts of the body like liver, heart, lungs etc.**

HEAVY METALS

- **HOW CAN THEY CAUSE ARTHRITIS ?**
- **= They cause generation of free radicals , autoimmune rxn of B and T lymphocytes that affects the synovium.**
- **=They cause increase in cytokines generation and entry into affected joints and increase in inflammation**

TYPES OF ARTHRITIS

- OSTEO ARTHRITIS
- RHEUMATOID ARTHRITIS
- GOUT ARTHRITIS

HEAVY METALS AS HUMAN CASINOGEN

- **Mechanism of Action:**
- **Distortion of DNA conformation during replication and transcription**
- **Mutational activation of protooncogenes and/or inactivation of tumor suppressor genes**
- **Clonal expansion of pre-malignant cells**

BIOIMPORTANCE OF SOME METALS AS TRACE ELEMENTS

- Needed in very minute amount e.g Zn, Mg, molybdenum, Cr etc. found in some enzymes
- Fe and Ca needed in fairly large amount

LEAD

- Sources
- Uses
- Exposure/Contamination
- Organs affected
- CNS , Kidney, Liver, Immune system
etc.

LEAD CASINOGENICITY/ TOXICITY

- Direct DNA damage
- DNA synthesis inhibition
- Clastogenicity
- Generation of free radicals (Arthritis)
- Pb can substitute for Zn in several enzymes in DNA replication leading to altered gene expression

MERCURY

- Exist as sulphide
- HUMAN EXPOSURE
- Mining , industries, paint ,electrical wks
- Hg classified by IARC as CLASS 3 CASINOGEN

NICKEL

- HUMAN EXPOSURE
- TOXICITY/CANCER:
- **Inhibition of intercellular communications**
- **Immortalization of fibroblasts and epith. Cells**
- **Induction of DNA deletions and aberrations**
- **Oxidative damage which also causes Arthritis**
- (Miki et al 1987, Biedermann and Landolph, 1987,
• Patierno SR, Dirscherl L, Xu J 1993, Costa M, 1996))

BENEFICIAL EFFECT OF NICKEL

- Trace Element by WHO
- Enzymes containing nickel in plants and animals (WHO, 1996)

ARSENIC

- SOURCE
- HUMAN EXPOSURE
- From commercial appl. In semiconductors, wood preservatives, non ferrous alloy, glass, insecticide
- UNDERGROUND WATER CONTAMINATION

ARSENIC TOXICITY

- CACINOGENICTY
- **By alteration in cell differentiation and proliferation:** thro. Increased cellular tyrosine phosphorylation
- (Leonard and Gerber 1994; Hayes, 1997; Hayes ,1997).

CADMIUM

- SOURCE:
- T $\frac{1}{2}$10-30 yrs
- TOXICITY:
- Accumulates in kidney = tubular dysfunx
- Displaces Zn in biological rxn in synthesis of DNA and RNA (**Brzóska and Moniuszko, 2001**)
- Induces single stranded DNA break
- Inhibits DNA repair
- Activates pro-oncogens. (**McMurray and Tainer, 2003; Waalkes ,2000; Abshire et al,1996**)

COBALT

- Trace element contained in Vit B (cyanocobalamin)
- Essential in DNA synthesis
- **CASINOGENICTY:**
- **Causes production of fibrosarcoma, rhabdomyosarcoma etc.**
- **IARC status..... Can be casinogenic**

COBALT EXPOSURE

- In metal smelting
- In alloys..... Steel, magnet
- Orthopaedic implants.....(cobalt-chromium-molybdenum-nickel alloy)

IRON (Fe)

- **SOURCE:** = earth
- **EXPOSURE:=** Agric product, meat, sea foods, smelting and arc welding
- **TOXICITY:**
- Rare in human
- **In animal model:** high dose= sarcoma attributed to Fe CHO complex

ARTHRITIS AND Fe

- Increases RA through prod. of OH- radicals.
- By ferrous ion promoting hyaluronic acid break down in the joints

BORON ...A CONTRAST

- **DEMOGRAPHY STUDY= BY NEUNHAM (1986)**
- **SOILS/REGIONS = WITH BORON DEFF. SUFER RA more**
- **REGIONS = WITH HIGH BORON HAS LESS ARTHRITIS**

MECHANISM OF ACTION

- **BORON = acts as cell membrane catalyst allows ions to enter cells and on this basis ATP.(loughman 1983)**
- **Cartilage / collagen cells regenerate**
- **RA Overcomed**
- **Anti- infective == low conc. Inhibits bacteria**

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