NEUROTOXICITY IN CADMIUM-EXPOSED WORKERS

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[Neurotossicità in lavoratori esposti al cadmium]

ABSTRACT

Cadmium (Cd) is a major toxic metal. It is present in soils, sediments, air and water. Unlike most metals, the cadmium use has developed recently and it has large-scale application. The target organs for Cd toxicity in animals include the liver, kidney, lungs, testes, prostate, heart, skeletal system, immune and nervous systems.

Nervous system damage induced by Cd are represented by peripheral polyneuropathy and lesions of the basal ganglia leading to parkinsonism and more generally to psychological disorders. The neurotoxic effects described are due to damage of both peripheral and central nervous system. The highly toxic heavy metals, such as cadmium, are environmentally and occupationally widespread pollutants with mutagenic, carcinogenic, and teratogenic effects. This metal belongs to the most harmful factors due to their tendency to accumulate in tissues and organs and to transfer along food chains, high reactivity, and the ability to stimulate reactive oxygen species (ROS) formation and to produce injury in cell functions.

Key words: Cadmium, smokers, astrocytes, neurodegeneration.

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Introduction

Cadmium (Cd) is a major toxic metal and represents an increasing risk for cancer as a pollutant of the environment at large. Inhalation of Cd fumes or dust is the main route in occupational exposure to Cd[(1)].

Major occupational exposure occurs in non-ferrous metal smelters, in the production and processing of cadmium, its alloys and compounds and, increasingly, in the recycling of electronic waste. Non-occupational exposure, instead, is mainly related to cigarette smoke which contains relatively high concentrations of this element; for non-smokers who are not occupationally exposed, diet is the main route of exposure to cadmium[(2, 3)].

Most Cd is used for the production of batteries, especially Ni-Cd; it is partly used in the plating of surface protection of metal materials such as steel, Fe and Cu. Cadmium salts are used in photography and in the manufacture of fireworks, tires, fluorescent paint, glass and porcelain, for the production of electric storage batteries and equipment for radio and television.

Cigarette smoke is a major source of cadmium exposure. Biological monitoring of cadmium in the general population has shown that cigarette smoking may cause significant increases in blood cadmium levels; the concentrations in smokers being on average 4-5 times higher than those in non-smokers[(4)].

The concentration of cadmium in the blood or urine is a better indicator of cadmium exposure.

Urinary excretion of Cd is a biomarker of lifetime Cd exposure. Cd excretion in 24-h urine is rather stable in solute composition and is therefore the gold standard to measure Cd in the urine matrix.

The mean urinary Cd level in the US population averaged 0.18 μg/g creatinine. The Cd level in blood mainly reflects the past few months of exposure. Non-smoking adults living in non-polluted

areas have blood Cd concentrations that vary between 0.1 and 1.0 μg Cd/l in whole blood.

The toxicity of cadmium relates to smelting where the main route of exposure is through the lungs. Soluble cadmium salts accumulate and result in toxicity to the kidney, liver, lungs, brain, testes, heart and central nervous system.

Cadmium metabolism

Metabolism of toxic metals is often dictated by the essential elements they may mimic. Cadmium appears to mimic zinc and to a lesser extent calcium[5]. Experimental animal data indicate that a low intake of calcium, iron, zinc, and copper may increase the intestinal absorption of cadmium. In humans, iron status has been shown to influence its absorption in the gastrointestinal tract[6,7].

There is a common pathway for absorption of cadmium and iron through the divalent metal transporter-1 (DMT-1) which accounts for high accumulation of cadmium during iron deficiency[8].

In one study on the intake and uptake of cadmium in women with a preference for vegetarian or mixed diets, reduced body iron stores (serum ferritin) were highly associated with higher concentrations of cadmium in blood. Instead, animal experiments have indicated that the absorption of cadmium is inhibited by fiber, phytate and lignin[9, 10].

A high dietary intake of fiber may thus result in a lower rate of intestinal absorption of cadmium. This possibility may explain why the fairly high intake of cadmium with vegetarian diets is not reflected in a corresponding increase in concentration in the blood.

Cadmium has been shown to induce neurodegeneration carcinogenesis and anemia[11].

Exposure of neurons and astrocytes to cadmium can activate apoptotic cascades, provoke cell cycle arrest and interfere with cell signalling pathways. Chronic occupational exposure to Cd was found to influence the slowing of psychomotor functions and the increase of complaints about equilibrium and ability to concentrate. The neurotoxic effects described are due to damage of both peripheral and central nervous system.

The finding of signs of parkinsonism in retired Cd-exposed workers might be associated with genetic susceptibility.

Cadmium is a putative neurotoxicant; however, little attention has been paid to its neurotoxic risk for humans in the occupational setting.

Pathogenetic mechanism

Several hypothesis have been suggested to explain the molecular mechanisms of the neurotoxic action of the Cd ion, competition with Zn or Ca, interaction with nucleic acids, second messenger systems, enzymes, receptors or translocating proteins, effects on neurotransmitter concentrations and reuptake, disruption of membrane dynamics including the function of Ca channels and damage to glial cells resulting in accelerated lipoperoxidation that influences neuronal function[12].

In vitro studies

In vitro studies have revealed that acute or chronic Cd exposure enhances oxidative stress in astrocytes and accumulates reactive oxygen species (ROS) that induce astrocytic death[13].

Cd is reported to induce apoptosis via the activation of JNK-mediated signaling where Ca and oxidative stress act as the pivotal mediators of apoptotic signaling in skin epidermal cell line[14].

Cd may increase reactive oxygen species production in a catalytic fashion via redox cycling[15].

Oxidative DNA damage can interfere with the ability of methyltransferases to interact with DNA, thus resulting in a generalized hypomethylation.

Cd neurotoxicity in animals

Studies in rodents exposed to Cd showed behavioural changes and damage to the nervous system usually affecting only regions without the blood-brain barrier[16, 17].

Evidence for neurotoxicity of chronic exposure to Cd is fairly strong as shown in several studies on exposure to Cd during gestation or in neonatal or weanling animals.

They reported behavioural changes at a later stage in life, hyperactivity, increased locomotor and rearing activities or deficits in visual discrimination or learning[18]. During rat brain development Cd exposure induced hyperlocomotion, enhanced grip strength and reduced learning-memory functions[19].

Astrocytes play an important role in long-term potentiation that is considered as one of the major mechanisms that underlies learning and memory[20, 21].

Cd neurotoxicity in humans

Cd neurotoxicity can involve both peripheral and central nervous systems. Symptoms of fatigue, mental irritability, headache, muscle weakness, dizziness, syncope and hyposmia were reported in patients or workers acutely or chronically exposed to Cd[22, 23, 24].

Reports, in several cases, have described demyelinating polyneuropathy or some symptoms related to polyneuropathy[25].

Perinatal exposure to Cd induces anxiety and learning ability of offspring[26, 27].

Other symptoms are a decrease of motor speed, attention, memory vision for skills[28] and a presence of neurophysiological and neurobehavioural abnormalities.

In Cd-exposed children diminished intelligence was described especially with respect to verbal, psychomotor, cognitive and perceptual skills[29].

In case-control studies in which the hair concentration of Cd of a clinically defined group was compared with that of a reference group, higher concentrations were reported in children with mental retardation and learning difficulties or dyslexia[30, 31].

In cohort studies, Thatcher et al reported that the concentration of Cd in hair was inversely related to adjusted IQ[32, 33].

Marlowe et al[34] have reported associations between hair Cd and children's performance on visual motor tasks.

Conclusions

Neurotoxicity is a common health endpoint for Cd exposure. Co-administration of natural or synthetic antioxidants may improve the removal of Cd from the system as well as lead to better and faster clinical recoveries in animal models[35, 36].

Future investigations must address those neuronal mechanisms in detail in order to understand cadmium-induced neurotoxicity and its possible treatment[37, 38].

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