Effect of Cadmium Exposure on Zinc Levels in Normal Non-Diabetic and Diabetic Rats Induced by Streptozotocin

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Abstract
Diabetic rats induced by streptozotocin and normal non-diabetic rats were exposed to cadmium sulphate in drinking water at a dose of 200 mg / L for 30 days. At the end of the exposure, the blood, kidney and pancreas of each rat were taken for the determination of cadmium and zinc. The results show a significant increase in the level of cadmium in the blood, kidney and pancreas of normal non-diabetic rats and diabetic rats compared to the control group. The cadmium concentration was significantly higher in plasma and tissues in diabetic rats compared to normal non-diabetic rats. Cadmium poisoning resulted in a significant decrease in the level of zinc in the blood and tissues of normal non-diabetic rats and diabetic rats compared to their respective controls. This study reveals that diabetic rats induced by streptozotocin are more sensitive to the toxic effects of cadmium than normal rats.

Keywords: Cadmium, zinc, plasma, pancreas, kidneys, diabetes.

1 | INTRODUCTION

Cadmium (Cd) is an important nephrotoxic environmental pollutant, which possess increasing risks to populations in many parts of the world and Long-term exposure of Cd (7 μg cadmium/week/kg b/w) in humans and experimental animals induces kidney toxicity (1). Cd is found naturally in small quantities in air, water and soil and it can be released into the air when household or industrial waste, coal or oil is burned. Cd also can be released from car exhaust, metal processing industries, battery and paint manufacturing units, waste hauling and disposal activities. Higher levels of Cd may be found in soil or water near by the area of industrial and hazardous waste sites. Annual amount of Cd with industrial waste discharged into the environment was more than 680 tons) (2). Cd can enter into the body from smoking tobacco, contaminated air inhalation and Cd containing food and water intake. Fruits and vegetables, especially grains, potatoes and leafy vegetables like spinach, they may grow in soils with high levels of Cd, may contain elevated levels of Cd. Cadmium is a heavy metal that also refers to endocrine disrupting chemicals, having a special impact on the functioning of reproductive organs, including testes, placenta (3), and ovaries (4). The mechanisms of toxicity of Cd also include induction of oxidative and endoplasmic reticulum stress, inflammatory response (5, 6), genotoxicity (7, 8),
and interference with essential metals (especially zinc) (9).

Interactions of Cd with Zn can take place at different stages of the use of this trace element by our organism (absorption, distribution and excretion) and this can thus affect the biological functions of Zn (10). Zn is an excellent antioxidant which prevents the synthesis of free oxygen radicals which are responsible for oxidative stress (11). Zn is involved in the stabilization of the cell membrane, the synthesis of metallothionein (MT) and the structure of superoxide dismutase (SOD Cu / Zn) (12). The objective of this study is to assess the concentration of cadmium and zinc in the blood, pancreas and kidney in normal non-diabetic rats and in diabetic induced by streptozotocin.

2 | MATERIALS AND METHODS

2.1 | Animals and treatment

Twenty young male Wistar rats weighting between 209- 279 g were obtained from the Ecole Normale-Supérieured’Abidjan animal facility. These animals were housed at the Pasteur Institute animal care facility in plastic cages and a cycle of day/night was maintained (approximately 12 hours of light and 12 hours of darkness) in a ventilated animal room. The rats were acclimated for 14 days to their new environment before the treatment and had free access to sterile distilled water and sterilized standard food. All the animals were handled in accordance with the guidelines and protocols approved by the Care and Use of Animals Committee of Côte d’Ivoire. Diabetes mellitus was induced in rats after one day fasting by intraperitoneal injection of a single dose of 60 mg / kg of body weight of streptozotocin (STZ) (Cayman Chemical, Michigan, USA) diluted in a freshly prepared citrate buffer (0.1 mol / L, pH 4.5) (13, 14). Blood glucose levels were measured from the tail vein using an AccuChek Active® (Roche, GU, Germany) glucometer before and three days after the STZ injection, rats with blood glucose levels greater than 250 mg/dL were considered to be diabetic and used for experimental studies (15, 16). The rats were divided into four experimental groups (control, STZ-treated, Cd-treated and Cd + STZ-treated), each group is made of five rats. The control and STZ-treated groups received distilled water and the Cd- andCd + STZ-treated groups had distilled water enriched with cadmium sulphate (CdSO4) at 200mg/l (17, 18). After 30 days, the rats were euthanized, the blood, the left kidney and the pancreas of each rat were prelude for the determination of metals (renal and pancreatic) for the determination of zinc and cadmium.

2.2 | Preparation of renal and pancreatic homogenates

The left kidney and pancreas of each rat were removed and placed in normal saline. The kidney and pancreas were homogenized with potassium phosphate buffer (0.1 M, pH 6.8) in mortar on an ice bucket. After centrifugation at 10,000 g for 20 minutes at 4 °C, the supernatant was collected and aliquoted in Eppendorf tubes and then stored at -20 °C for the quantification of metals in the kidneys and pancreas (19).

2.3 | Metals analyses (cadmium and zinc) in the renal and pancreatic homogenates

The cadmium and zinc were assayed at the Institute National Polytechnique Houphouët-Boigny by Flame Atomic Absorption Spectrometry using a Varian AA20 device as described Gbétoh et al. (20). The previously thawed samples were digested using a solution of hydrochloric acid (0.1M) in specific assay tubes so that their concentration was within the calibration range. The Air-Acetylene flame at 3000°C was used for the atomization of the samples. The reading wavelengths of lead and zinc were re-
spectively 217 nm and 214.8 nm. The detection limit was 0.001 mg/L, ie 1 µg/mL. The concentration of lead and zinc was determined by means of calibration curves of each metal ion, from standard solutions with respective concentrations of 0.5; 1 and 2 mg/L. These solutions were prepared from 1000 ppm multi-standard solutions. The assay in a given sample was performed in triplicate.

2.4 | Statistical analysis

The statistical analyses were carried out by using the software Graph Pad Prism 5 Demo. The results are presented in the form of average ± SEM. The test of Student and the test of Anova were used for the comparison of the averages. A value of p < 0.05 was regarded as significant.

3 | RESULTS

3.1 | Cadmium Concentration in plasma, kidney and pancreas

The results of the relative Cd content in the pancreas, the kidneys and the plasmas not being statistically different between the male rats of the same exposure group, the data concerning the males were compiled in Figure 1. The concentration of Cd in plasma, kidney and pancreas of the STZ group was not statistically different from that of the controls. In rats of the Cd group, the concentration of Cd increased highly significantly in the plasma, the pancreas and in the kidney (p <0.01) compared to the control groups. In diabetic rats drinking water enriched with cadmium sulphate (group STZ + Cd), cadmium caused a significant decrease in zinc levels in the plasma (p <0.05), very highly significant in the pancreas (p <0.001) and highly significant in the kidney (p <0.01) compared to the control group (STZ group).

3.2 | Effect of cadmium on zinc levels in plasma, kidney and pancreas

The results of the relative zinc content in the pancreas, the kidneys and the plasmas not being statistically different between the male rats of the same exposure group, the data concerning the males were compiled in Figure 2.

The non-diabetic rats contaminated with cadmium (group Cd) recorded a highly significant decrease in the level of zinc in the plasma, the pancreas and the kidney (p< 0.01) compared to the control groups. In diabetic rats drinking water enriched with cadmium sulphate (group STZ + Cd), cadmium caused a significant decrease in zinc levels in the plasma (p <0.05), very highly significant in the pancreas (p <0.001) and highly significant in the kidney (p <0.01) compared to the diabetic control rat (STZ group).
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4 | DISCUSSION

In this study, rats with streptozotocin-induced diabetes who were drinking water enriched in cadmium sulfate for 30 days had higher cadmium concentrations in plasma, pancreas, and kidney compared to non-diabetic rats contaminated with cadmium. This significant increase in Cd concentration is due to an increase in water consumption and a reduction in the excretion of cadmium in the urine \( (21) \). In addition, cadmium contractions in the kidneys of experimental rats were greater than that of the pancreas. This is explained by the fact that the kidney is the main organ for the accumulation of cadmium in animals \( (22, 23) \).

Cadmium has caused a significant decrease in the concentration of zinc in the blood and pancreas in non-diabetic and diabetic animals. Indeed, in biological systems, Interactions of Cd with Zn can take place at different stages of the use of this trace element by our organism (absorption, distribution and excretion) and this can thus affect the functions of Zn \( (10) \).

In biological systems Cd and Zn are linked to macromolecules, primarily through sulphur (S), oxygen (O) and nitrogen (N) and interact readily with S-, O- and N-donors. They bind preferentially to the same proteins - albumin in the bloodstream and metallothionein (Mt) and other proteins in tissues. Although both metals have a high affinity to biological structures (proteins, enzymes) containing –SH (sulphydryl) groups, the affinity of Cd to S-ligands as well as to N-donors is greater than that of Zn \( (23, 24) \). Thus Cd\(^{2+}\) and Zn\(^{2+}\) ions can compete for uptake into various cells and binding to intracellular sites and Cd may displace Zn in a number of biological processes \( (25, 26) \). In this way, one of the metals can influence the uptake and action of the other, depending on their levels. The mechanisms of the interactions are widely debated, being competitive \( (25, 26) \) or non-competitive \( (25) \), depending on the experimental model. Several studies have suggested that interactions between Cd and Zn in the organism result in a high degree from an affinity of both metals to Mt and their ability to induce its synthesis. They can induce Mt synthesis in various tissues, especially in the intestine, liver and kidney \( (27, 28) \). Cd is about eight times more potent than Zn in increasing hepatic Mt concentration \( (29) \).

5 | CONCLUSION

Diabetic rats induced by streptozotocin are more sensitive to the toxic effects of cadmium than normal rats.

6 | CONFLICT OF INTEREST

7 | ACKNOWLEDGEMENTS

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