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Effect of cadmium chloride exposure during the induction of collagen induced arthritis

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ABSTRACT

The precise cause of autoimmune diseases such as rheumatoid arthritis remains uncertain. Collagen induced arthritis (CIA) in animals is the most commonly used model of human rheumatoid arthritis (RA). Exposure of humans and animals to toxic metals is widespread. Cadmium is one of the most prevalent nephrotoxic heavy metal, but it may cause other systemic toxicity as well. Cadmium may cause adverse health effects by impairment of the immune systems and induction of reactive oxygen species. Since rheumatoid arthritis pathogenesis involve immune system disorder and chronic inflammation, the present study has been designed to find out the effect of cadmium chloride exposure on clinical manifestation of development of collagen induced rheumatoid arthritis. Arthritis was induced in rats by intradermal injection of emulsion of type II collagen in Complete Freund's Adjuvant. Rats were treated with cadmium chloride dissolved in drinking water at concentrations of 5 ppm and 50 ppm for 21 days from day of immunization. The effects of cadmium in the rats were assessed by biochemical parameters (articular elastase, articular nitrite, lipid peroxidation, reduced glutathione, catalase and superoxide dismutase) histopathological analysis and immunohistochemical expression of pro-inflammatory cytokines in rat joint tissue. Histopathological changes further confirmed the biochemical and immunohistochemical results. Our results suggest that exposure to cadmium chloride during the induction phase of collagen induced arthritis abrogate disease development at lower dose whereas exacerbates at higher dose in Wistar rats.

1. Introduction

The pathology of rheumatoid arthritis (RA) is characterized by the proliferation of synovial cells, angiogenesis and pannus formation. Multiple cell types, including lymphocytes, dendritic cells, macrophages, and synovial fibroblasts, contribute to the chronic inflammatory responses of RA, and comprise a major portion of the invasive pannus [1]. The aetiology of disease has not been fully understood, but the inflammatory processes that result in RA are multifactorial, involving complex interactions among the cytokine network [2], autoantibodies [3] and the complement system [4]. There may be multiple causes of disease, but the most likely triggers are suspected to be an abnormal autoimmune response, genetic susceptibility and some biological or environmental triggers, such as a viral infection, hormonal changes or heavy metals [5].

Chronic health effects on the general population and occupational workers due to heavy metals are matters of prime concern. Numerous occupations can put an individual at risk of exposure to a particular metal. Cadmium (Cd) is a heavy metal pollutant and widely distributed in the environment. Steel industry, waste incineration and zinc production account for the largest emissions of atmospheric Cd whereas waste disposal is the largest source of Cd to land [6]. Cd concentrations in food normally range from 2 to 100 ppb and can reach levels that exceed 1 ppm in cigarette smoke [7]. Smoking has been recognized as a significant risk factor in RA [8]. Major toxicity of Cd is due to its accumulation in the kidney. Renal dysfunction results in proteinuria, glycosuria, renal hypertension and other metabolic disorders [9]. Cd may also cause adverse health effects by impairment of the immune system, disrupting the endocrine system and induction of reactive oxygen species (ROS) [10]. Cd affects the immune system by modulating humoral or cellular response [11] and impairs both phagocyte and lymphocyte functions in vitro [12].

Reports by various researchers showed that Cd is not redox active heavy metal [13,14] and acts as immunomodulator [7,15].

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To the best of our knowledge, there is no such report or data available which has shown the effect of Cd on development of collagen induced arthritis that demonstrate how the cadmium exposure from day of immunization affect dose dependently on development of arthritis. The selected dose level of cadmium for the present study is based on earlier findings [16] where cadmium chloride at 5 ppm is reported to inhibit humoral and cellular immune response whereas at 50 ppm, cadmium chloride exposure enhanced the effect. Therefore, the present study was designed to explore dose dependent effect of Cd on the development of collagen induced arthritis.

2. Materials and methods

2.1. Chemicals

Complete Freund's Adjuvant (CFA), Cadmium Chloride was purchased from Fluka USA, N-methoxysuccinyl-Ala-Ala-Pro-Val p-nitroanilide and Griess Reagent systems were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Collagen type II from bovine nasal septum was purchased from Elastin Products Co, Inc., Owensville, Missouri, USA. Poly-HRP plus ONE detection System (Thermo Scientific), thiobarbituric acid (TBA), trichloroacetic acid (TCA), 5-5′dithio-bis-2-nitrobenzoicacid (DTNB), nitrobluetetrazolium (NBT), ethylene diamine tetra-acetic acid (EDTA), xanthine, xanthine oxidase, tris hydrochloride were purchased from SD Fine Chemicals India. All other routine chemicals used in this investigation were of research grade.

2.2. Animals

Female Wistar rats (150–170 g), 6–8 weeks old, were obtained from the Central Animal House Facility of Hamdard University (New Delhi, India). Rats were housed in groups of six animals per cage at ambient temperature of 25 ± 1 °C with 12 h light/dark cycles after initial acclimatization for about 1 week. They had free access to standard rodent pellet diet and water ad libitum. Animals received humane care in accordance with the guideline of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India, and prior permission obtained from the Institutional Animal Ethics Committee (IAEC No.:173/CPCSEA, 28 January 2000).

2.3. Experimental procedure

Rats were randomly divided into four groups of six rats each and dose decided according to previous studies [16]. Group I received water supply from the State Company (the CdCl2 concentration was of 0.0001 mg/L) to use it as control. Group II served as CIA group. Group III served as CIA plus CdCl2 treated (5 ppm in drinking water from day of induction). Group IV served as CIA plus CdCl2 treated (50 ppm in drinking water from day of induction) group and the uptake of CdCl2 was monitored in the experimental groups in an objective manner by determining the volume of water drunk by the animals. Daily average uptake of water was 180 ml by each group. This experimental design is summarized in Fig. 1.

2.4. Induction of collagen-induced arthritis (CIA)

Arthritis was induced in rats as described previously [17]. Collagen Type II from the bovine nasal septum was dissolved in 0.05 M acetic acid at a concentration of 2 mg/ml and emulsified with an equal volume of Complete Freund's Adjuvant (CFA) containing 1 mg/ml *Mycobacterium tuberculosis* H37 RA and stored on ice before use. Rats were immunized intradermally at about 1.5 cm distal from the base of the tail.

2.5. Measurement of clinical severity of arthritis

To examine the severity of disease, paw thickness was measured before and after the onset of the disease daily with a digital calliper (YAMAYO, Japan). Evaluation of joint inflammation was performed by an observer having no knowledge of the treatment protocol. The severity of the arthritis was determined after every third day by a clinical score measurement [18] from 0 to 4 as follows: 0 = no macroscopic signs of arthritis; 1 = swelling of one group of joints (namely, wrist or ankle joints); 2 = two groups of swollen joints; 3 = three groups of swollen joints; 4 = swelling of the entire paw.

2.6. Preparation of cell-free extract of the knee joints

At the end of the experiment animals were anesthetized and sacrificed by cervical dislocation. Arthritic and non-arthritic joints were removed and cut into small pieces and homogenized in 5 vol.

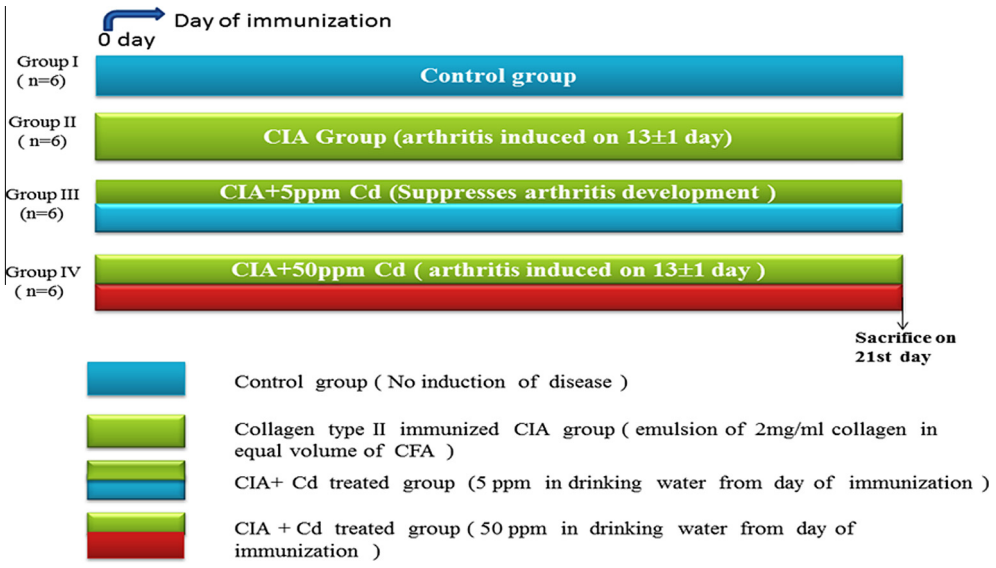

Fig. 1. Schematic representation of experimental design.