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Cadmium nitrate-induced neuronal apoptosis is protected by *N*-acetyl-L-cysteine via reducing reactive oxygen species generation and mitochondria dysfunction

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ABSTRACT

Cigarette smoking is a well-established risk factor for various diseases, such as cardiovascular diseases, neurodegeneration, and cancer. Cadmium nitrate ($Cd(NO_3)_2$) is one of the major products from the cigarette smoke. Up to now, no supporting evidence on $Cd(NO_3)_2$-induced apoptosis and its related working mechanism in neurons has been found. In present study, the mode of cell death, caspase activities, reactive oxygen species (ROS) generation, and mitochondrial dysfunction in N2a cells, which are neuron-like cells, were assessed by Annexin V-FITC and PI assays, caspase fluorometric assay, DCFH-DA fluorescence assay, and JC-1 fluorescence assay respectively. The results showed that not only $Cd(NO_3)_2$ induced apoptosis and necrosis but also the activities of caspase-3 and -9 expressed in a concentration-dependent manner. In addition, $Cd(NO_3)_2$ also induced both mitochondrial dysfunction and ROS generation in a concentration-dependent manner. All these indicated that in N2a cells parallel trends could be observed in apoptosis, caspase-3 and -9 activities, mitochondrial dysfunction, and ROS generation when induced by $Cd(NO_3)_2$. Furthermore, $Cd(NO_3)_2$-induced apoptosis, caspases activities, mitochondrial dysfunction, and ROS generation were reduced by *N*-acetyl-L-cysteine (NAC). These results indicated that $Cd(NO_3)_2$-induced neuronal apoptosis was reduced by NAC via intrinsic apoptotic caspase cascade activities and their up-stream factors, including mitochondrial dysfunction and ROS generation.

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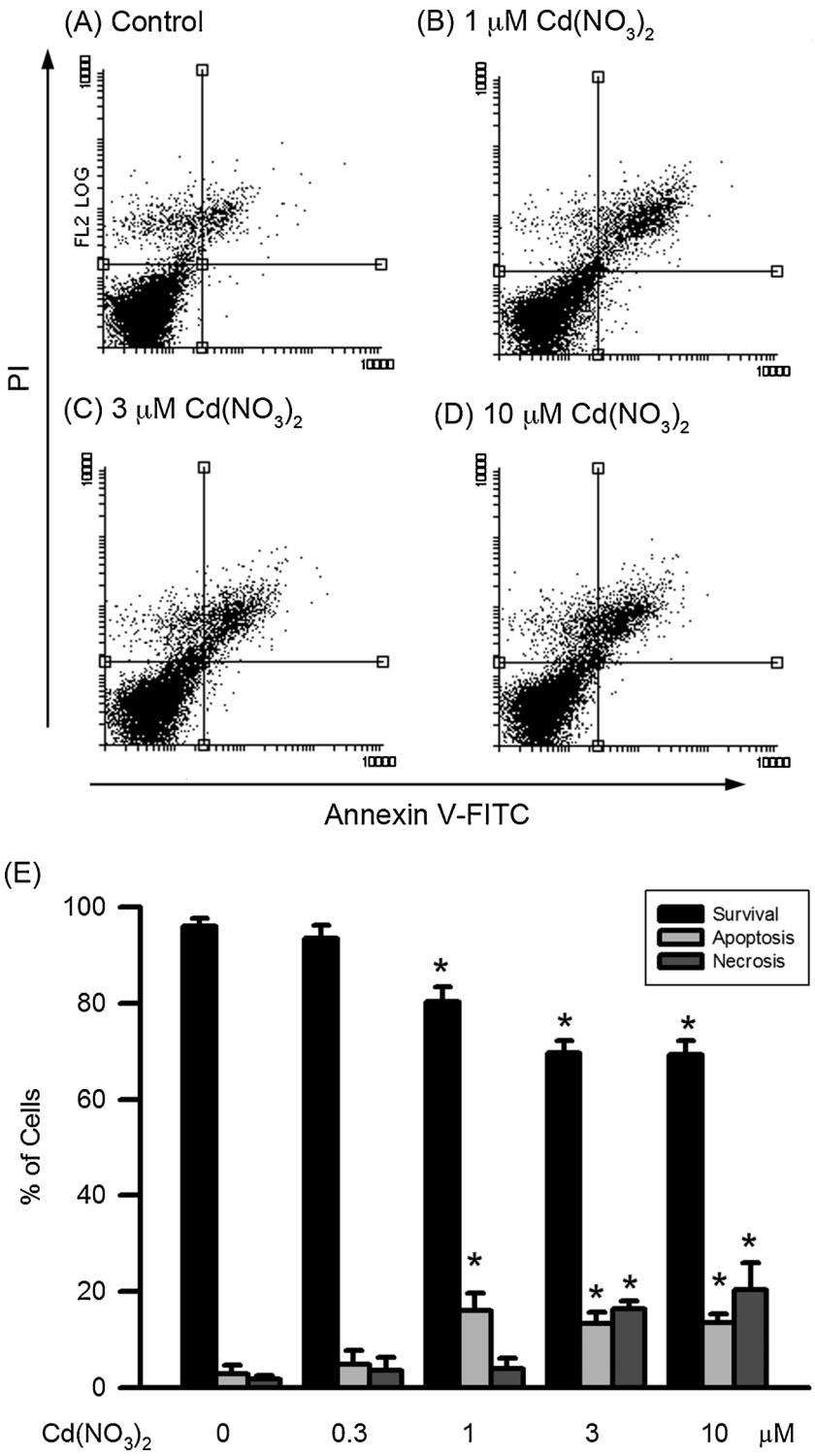

Fig. 1. $Cd(NO_3)_2$ induced apoptosis in N2a cells. The apoptosis was measured by Annexin V-FITC and PI assays using flowcytometry. Cells were incubated with $Cd(NO_3)_2$ at various concentrations of 0 (A), 0.3 (B), 1 (C), and 3 (D) μM for 24 h at 37 °C. The upper left quadrant (Annexin V−/PI+) is representative of necrosis; upper right and lower right quadrants (Annexin V+/PI+ and Annexin V+/PI−) are representatives of apoptosis; and lower left quadrant (Annexin V−/PI−) is representative of living cells. (E) Quantitatively, the percentage of necrotic cells, viable cells, and apoptotic cells were calculated and analyzed. Data are expressed as mean ± SD (n = 5). * $p < 0.05$ considers significant as compared with control group.

1. Introduction

Cadmium (Cd) exists in the crust of earth in about 0.1 part per million. It has been used in various industrial applications, such as in zinc or lead smelting, steel galvanizing, or in manufacturing of television screens, lasers, batteries, cosmetics, paint pigments, and phosphate fertilizers [1]. Although the products containing Cd can be recycled, Cd pollution is generated by smoking the cigarettes, dumping and incinerating the wastes contaminated with Cd [2]. Cd can be rapidly absorbed through skin, respiratory and gastrointestinal tracts, and biological membranes [3]. Kidney is the chief organ affected in Cd exposure and the induced toxic response is characterized by proximal tubule dysfunction [4]. Bone density is decreased by Cd due to hypercalciuria and impair vitamin D metabolism resulting from renal dysfunction [5]. Initiation and progression of atherosclerosis are promoted by Cd because of endothelial dysfunction, reactive oxygen species (ROS) generation, and acceleration of atherosclerotic plaque formation [6]. The International Agency for Research on Cancer Monographs has identified Cd and its related compounds as carcinogens to human (Group I), including lung, kidney, and prostate cancers [7].

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