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Research Article

Thimerosal-Derived Ethylmercury Is a Mitochondrial Toxin in Human Astrocytes: Possible Role of Fenton Chemistry in the Oxidation and Breakage of mtDNA

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Thimerosal generates ethylmercury in aqueous solution and is widely used as preservative. We have investigated the toxicology of Thimerosal in normal human astrocytes, paying particular attention to mitochondrial function and the generation of specific oxidants. We find that ethylmercury not only inhibits mitochondrial respiration leading to a drop in the steady state membrane potential, but also concurrent with these phenomena increases the formation of superoxide, hydrogen peroxide, and Fenton/Haber-Weiss generated hydroxyl radical. These oxidants increase the levels of cellular aldehyde/ketones. Additionally, we find a five-fold increase in the levels of oxidant damaged mitochondrial DNA bases and increases in the levels of mtDNA nicks and blunt-ended breaks. Highly damaged mitochondria are characterized by having very low membrane potentials, increased superoxide/hydrogen peroxide production, and extensively damaged mtDNA and proteins. These mitochondria appear to have undergone a permeability transition, an observation supported by the five-fold increase in Caspase-3 activity observed after Thimerosal treatment.

1. Introduction

1.1. Thimerosal and Ethylmercury. Thimerosal is a preservative that is widely used in medical products, including as a preservative in vaccines, immunoglobulin preparations, skin test antigens, antivenins, ophthalmic and nasal products, and tattoo inks, and is composed of 49.6 percent ethylmercury by weight [1]. The widespread use of Thimerosal exposes many to its potential toxic effects, especially *in utero* and in neonates. We report the results of a series of experiments using cultured normal human astrocytes (NHA) exposed to Thimerosal to study the compound's effect on astrocyte mitochondria.

1.2. Oxidative Stress and Brain. The brain utilizes 20% of the oxygen consumed by the body but constitutes only 2% of the body's mass [2]. Some 5% of molecular oxygen consumption may arise from its reduction to superoxide [3]. The majority of superoxide generated in cells comes from the reaction of molecular oxygen with flavin or quinone radicals, which are partly generated during respiration within complexes of the mitochondrial respiratory chain [4]. The rate of reactive oxygen species (ROS) production increases steeply with increased mitochondrial membrane potential [3]. Superoxide has a very short half-life in cells as it is rapidly dismutased by either the cytosolic Cu-Zn superoxide dismutase (SOD) or the Mn-SOD in the mitochondrial matrix, producing molecular oxygen and hydrogen peroxide. Thus, generation of superoxide is always accompanied by hydrogen peroxide production, and so opens up the possibility of hydroxyl radical ($HO^{\bullet}$) generation via Fenton/Haber-Weiss chemistry [5]. Fenton metals, including iron and copper, catalyze the production of $HO^{\bullet}$ from superoxide/hydrogen peroxide and so the free, unchelated levels of transition metals inside cells are very low and normally all stored in an oxidized