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Novel Lipid-Soluble Thiol-Redox Antioxidant and Heavy Metal Chelator, *N,N'*-bis(2-Mercaptoethyl)Isophthalamide (NBMI) and Phospholipase D-Specific Inhibitor, 5-Fluoro-2-Indolyl Des-Chlorohalopemide (FIPI) Attenuate Mercury-Induced Lipid Signaling Leading to Protection Against Cytotoxicity in Aortic Endothelial Cells

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Abstract

Here, we investigated thiol-redox-mediated phospholipase D (PLD) signaling as a mechanism of mercury cytotoxicity in mouse aortic endothelial cell (MAEC) in vitro model utilizing the novel lipid-soluble thiol-redox antioxidant and heavy metal chelator, *N,N'*-bis(2-mercaptoethyl)isophthalamide (NBMI) and the novel PLD-specific inhibitor, 5-fluoro-2-indolyl des-chlorohalopemide (FIPI). Our results demonstrated (i) mercury in the form of mercury(II) chloride, methylmercury, and thimerosal induced PLD activation in a dose- and time-dependent manner; (ii) NBMI and FIPI completely attenuated mercury- and oxidant-induced PLD activation; (iii) mercury induced upstream phosphorylation of extracellular-regulated kinase 1/2 (ERK1/2) leading to downstream threonine phosphorylation of PLD₁ which was attenuated by NBMI; (iv) mercury caused loss of intracellular glutathione which was restored by NBMI; and (v) NBMI and FIPI attenuated mercury- and oxidant-induced cytotoxicity in MAECs. For the first time, this study demonstrated that redox-dependent and PLD-mediated bioactive lipid signaling was involved in mercury-induced vascular EC cytotoxicity which was protected by NBMI and FIPI.

Keywords

mercury; vasculotoxicity; PLD; endothelial cell; NBMI; thiol redox; antioxidant; FIPI; mercaptoethylisophthalamide; bioactive lipid signaling

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Declaration of Conflicting Interests

Boyd E. Haley, a coauthor of this communication, is Professor Emeritus in the Department of Chemistry at the University of Kentucky, Lexington, KY, USA with a 20% research appointment and is on an active NSF grant in that institution. Dr Haley is also the President of CTI Science which is a possible conflict of interest since they hold the license to the patents concerning the compound, NBMI. However, this research project had not been funded or had not been supported or carried out in part or full by CTI Science in any way. Neither Dr Haley nor CTI Science had any influence or control on this research project. This research project was entirely initiated and supervised by Narasimham L. Parinandi at the Ohio State University, Columbus, OH, USA, with the compound, NBMI synthesized by Niladri Gupta (a graduate student of Boyd E. Haley) in the Department of Chemistry at the University of Kentucky, Lexington, KY, USA, under the supervision of Dr Haley. Boyd E. Haley is Chair of the Scientific Advisory Committee of the International Academy of Oral Medicine and Toxicology (IAOMT), who advises the IAOMT Board regarding scientific matters, but he does not have any control over IAOMT in their grant funding decisions. The IAOMT award has been given exclusively to Narasimham L. Parinandi to conduct research without any influence or control of Boyd E. Haley on this research project. Overall, there are no conflicts of interest.