

BCL-XL expression levels influence differential regional astrocytic susceptibility to 1,3-dinitrobenzene

Amanda D. Phelka^a, Margaret M. Sadoff^b, Bradley P. Martin^a, Martin A. Philbert^{a,*}

^a*Toxicology Program, Department of Environmental Health Sciences, University of Michigan, 1420 Washington Heights, Ann Arbor, MI 48109-2029, USA*

^b*Air Toxics Unit, Department of Environmental Quality, State of Michigan, Lansing, MI, USA*

Abstract

The selective vulnerability of brainstem astrocytes to 1,3-dinitrobenzene is mediated by a 10-fold lower threshold for opening of the cyclosporin A-inhibitable mitochondrial permeability transition pore (mtPTP). BCL-XL, BAX and BCL-2 are members of the BCL-2 protein family known to regulate both apoptotic and necrotic cell death signaling at the mtPTP. The levels at which these proteins are expressed relative to one another, where in the cell they are located and whether they are post-translational modified contributes greatly to the balance in active agonistic to active antagonistic BCL-2 proteins, and this critical balance has been hypothesized to dictate regional astrocytic susceptibility to DNB. The effects of DNB on the balance in expression of the BCL-2 family proteins have been evaluated in F344 rat DNB-sensitive (brainstem) and non-sensitive (cortical) tissue homogenates and primary astrocytes. No significant treatment-related alterations in BCL-XL, BAX or BCL-2 protein expression are observed in rat tissue homogenates or primary astrocytes. However, moderate increases in BCL-XL are observed only in DNB-treated rat cortical astrocytes, and these increases may be sufficient to shift the constitutive balance in expression of antagonistic to agonistic BCL-2 proteins from a ratio which favors BAX to one in which BAX and BCL-XL are comparably expressed. Rat primary brainstem and cortical astrocytes are also transiently transfected with *bcl-xl* to evaluate whether or not moderate enhancement of BCL-XL protein expression levels are sufficient to alter regional sensitivity to DNB in vitro. BCL-XL overexpression minimizes DNB-induced inhibition of succinate dehydrogenase (complex II) activity and increases significantly the concentration of DNB required to induce MPT onset in primary brainstem and cortical astrocytes. Results from the current investigation suggest that modest region-specific alterations in the balance in expression of antagonistic to agonistic BCL-2 proteins may adequately explain differential regional sensitivity to DNB-induced mitochondrial dysfunction.

Keywords: BCL-XL; Astrocytes; Dinitrobenzene