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Boric Acid Activation of eIF2α and Nrf2 Is PER Mechanism that Explains How Boron Prevents Enhances Antioxidant Status.

Yamada KE[1], Eckhert CD[2,3].

Author information

1 Interdepartmental Program in Molecular Toxicology, University of California, Los Angeles, 90095, CA, USA.

2 Interdepartmental Program in Molecular Toxicology, University of California, Los Angeles, 90095, CA, USA. ceckhert@ucla.edu.

3 Department of Environmental Health Sciences, Fielding School of Public Health, University of California, 650 Charles E. Young Dr., Los Angeles, CA, 90095, USA. ceckhert@ucla.edu.

Abstract

Boron is abundant in vegetables, nuts, legumes, and fruit and intake is associated with reduced risk of cancer and DNA damage and increased antioxidant status. Blood boric acid (BA) levels are approximately 10 μM BA in men at the mean US boron intake. Treatment of DU-145 human prostate cancer cells with 10 μM BA stimulates phosphorylation of elongation initiation factor 2α (eIF2α) at Ser51 leading to activation of the eIF2α/ATF4 pathway which activates the DNA damage-inducible protein GADD34. In the present study, we used MEF WT and MEF PERK (±) cells to test the hypothesis that BA-activated eIF2α phosphorylation requires protein kinase RNA-like endoplasmic reticulum kinase (PERK) and activates Nrf2 and the antioxidant response element (ARE). BA (10 μM) increased phosphorylation of eIF2α Ser51 in MEF WT cells at 1 h, but not in MEF Perk -/- cells exposed for as long as 6 h. GCN2 kinase-dependent phosphorylation of eIF2α Ser51 was activated in MEF PERK -/- cells by amino acid starvation. Nrf2 phosphorylation is PERK dependent and when activated is translocated from the cytoplasm to the nucleus where it acts as a transcription factor for ARE. DU-145 cells were treated with 10 μM BA and Nrf2 measured by immunofluorescence. Cytoplasmic Nrf2 was translocated to the nucleus at 1.5-2 h in DU-145 and MEF WT cells, but not MEF PERK -/- cells. Real-time PCR was used to measure mRNA levels of three ARE genes (HMOX-1, NQO1, and GCLC). Treatment with 10 μM BA increased the mRNA levels of all three genes at 1-4 h in DU-145 cells and HMOX1 and GCLC in MEF WT cells. These results extend the known boric acid signaling pathway to ARE-regulated genes. The BA signaling pathway can be expressed using the schematic [BA + cADPR → cADPR-BA → $[[ER]_i\ Ca^{2+}\downarrow]$ → 3 pathways: PERK/eIF2αP → pathways ATF4 and Nrf2; and $[[ER]_i\ Ca^{2+}\downarrow]$ → ER stress → ATF6 pathway. This signaling pathway provides a framework that links many of the molecular changes that underpin the biological effects of boron intake.

KEYWORDS: ARE; Boric acid; Boric acid signaling pathway; Boron; DNA damage; GCLC; HMOX; NQO1; Nrf2; Oxidative damage; PERK; eIF2α

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