S33-3 Lead induces the endoplasmic reticulum stress response in vascular endothelial cells

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Lead, a ubiquitous heavy metal, is an important industrial and environmental pollutant that can target the vascular endothelium. To clarify the effects of lead on the unfolded protein response (UPR) and their significance in cytotoxicity, we examined the expression and function of endoplasmic reticulum (ER) chaperones glucose-regulated protein 78 (GRP78) and 94 (GRP94) in vascular endothelial cells. We used bovine aortic endothelial cells as an in vitro model of the vascular endothelium. Exposure of the cells to lead nitrate resulted in a marked induction of GRP78 and GRP94 protein expressions in a dose- and time-dependent manner. GRP78 and GRP94 mRNA levels were also significantly increased in response to lead exposure. In addition, siRNA-mediated knockdown of GRP78 significantly enhanced lead-induced cytotoxicity. Compared with other metal(loid)s including cadmium chloride, zinc sulfate, copper sulfate, and sodium arsenite, lead nitrate was found to be the most potent metal to induce these chaperones in endothelial cells. In the examined UPR pathways, lead increased the phosphorylation of IRE1 and JNK. Interestingly, lead-induced up-regulation of GRP78 and GRP94 was almost completely blocked by JNK inhibitor SP600125 or AP-1 inhibitor curcumin. Taken together, these results suggest that lead induces ER stress but that induction of GRP78 and GRP94 expression via JNK/AP-1 pathway functions as a defense mechanism against cytotoxicity in vascular endothelial cells.