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COPPER INDUCES THE PRODUCTION OF NITRIC OXIDE AND PEROXYNITRITE IN VIVO

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We have previously shown that copper can modulate the activity of different isoforms of NOS in cell culture models. Here, we show how copper affects the pathway of NO in vivo. The administration of LPS (2 mg/ kg; i.v) or copper-histidine (CU-IST, 100 mM) elicited a time dependent fall in mean arterial pressure of rats. No significant alteration in the mean arterial pressure was observed in the saline-treated rats. NO levels were also significantly increased in the plasma obtained from rats challenged with LPS or CU-IST. A significant increase in iNOS gene expression was observed in thoracic aorta from copper-treated rats. In the cellular model of human umbilical cord vein endothelial cells, copper was found to strongly inhibit the production of NO due to constitutive eNOS.
Gen expression and enzymatic activity of inducible NOS was also significantly enhanced in lungs obtained 4 h after administration of LPS or CU-IST . Immunohistochemical analysis of lung sections obtained from LPS-treated rats or from CU-IST- treated rats revealed a positive staining for iNOS. Immunohistochemical analysis of lung sections obtained from rats treated with LPS or with CU-IST also revealed a positive staining for nitrotyrosine. There was no staining for either iNOS or nitrotyrosine in lungs obtained from the sham group of rats. Histological examination of lung sections of rats treated with LPS or with CU-IST showed oedema, tissue injury as well as infiltration of the tissue with PMNs, lymphocytes and plasma cells. No significant histological alteration was observed in the lugs from sham-treated rats. As a whole, our results provide evidence that copper induces the expression of iNOS, the production of NO and the formation of peroxynitrite, with consequent dramatic fall of arterial pressure and tissue damage. Copper could possibly switch on iNOS production through inhibition of constituitve isoforms of NOS.