

J1**Differential Effect of Copper (II) on the Cytochrome P450 Enzymes and NADPH-Cytochrome P450 Reductase: Inhibition of Cytochrome P450-Catalyzed Reactions by Copper (II) Ion**Joon-Sik Kim^{*1}, Taeho Ahn², Sung-Kun Yim³, and Chul-Ho Yun^{*2,3}¹AngioLab, ²Research Institute of Natural Science, and ³Department of Genetic Engineering, Pai-Chai University, Taejon 302-735, Republic of Korea

Inhibitory effects of Cu^{2+} on the cytochrome P450 (P450)-catalyzed reactions of liver microsomes and reconstituted systems containing purified P450 and NADPH-P450 reductase (NPR) were seen. However, Zn^{2+} , Mg^{2+} , Mn^{2+} , Ca^{2+} , and Co^{2+} had no apparent effects on the activities of microsomal P450s. Cu^{2+} inhibited the reactions catalyzed by purified P450s 1A2 and 3A4 with IC_{50} values of 5.7 and 8.4 μM , respectively. Cu^{2+} also inhibited reduction of cytochrome c by NPR (IC_{50} value of 5.8 μM). Copper caused a decrease in semiquinone levels of NPR although it did not disturb the rate of formation of semiquinone. P450 reactions supported by an oxygen surrogate, tert-butyl hydroperoxide, instead of NPR and NADPH, were inhibited by the presence of Cu^{2+} . The results indicate that Cu^{2+} inhibits the P450-catalyzed reactions by affecting both P450s and NPR. It was also found that the inhibition of catalytic activities of P450s by Cu^{2+} involves overall conformational changes of P450s and NPR, investigated by CD and intrinsic fluorescence spectroscopy. These results suggest that the inhibitory effect of Cu^{2+} on the P450-catalyzed reactions may come from the inability of an efficient electron transfer from NPR to P450 and also the dysfunctional conformation of NPR and P450. [This work was supported by Korea Research Foundation Grant (KRF-2000-015-FS0002)]