

Stoichiometry and conditional stability constants of Cu(II) or Zn(II) clioquinol complexes; implications for Alzheimer's and Huntington's disease therapy

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Successful trials with 5-chloro-7-iodo-8-hydroxyquinoline (clioquinol, CQ) for Alzheimer's disease treatment prompted renewed interest in assessing whether its therapeutic action is related to the coordination of neurotoxic trace metals, such as Cu(II) and Zn(II). We now report conditional stability constants (K_C) for CQ Cu(II) and Zn(II) complexes measured in a biological buffer containing Ca(II) and Mg(II) ions. UV-vis spectroscopy and polarography evidenced a 1:2 stoichiometry of Cu(II) and Zn(II) CQ complexes; the K_C s calculated were: $\text{Cu}(\text{CQ})_2$ 1.2×10^{10} , and $\text{Zn}(\text{CQ})_2$ $7.0 \times 10^8 \text{ M}^{-2}$; the CQ affinity for Cu(II) is at least an order of magnitude higher than for Zn(II). To test the possible functional relevance of the Cu(II) CQ complexes in the brain, we bioassayed free Cu(II) concentration by the metal-induced inhibition of ATP-gated currents of the P2X₄ receptor, a predominant brain P2X receptor. CQ reduced concentration-dependently the Cu(II) inhibition of the ATP-gated currents. In