

Complex formation equilibria of Cu^{II} and Zn^{II} with triethylenetetramine and its mono- and di-acetyl metabolites.

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Streszczenie

Triethylenetetramine (TETA) dihydrochloride, or trientine, is a therapeutic molecule that has long been used as a copper-chelating agent for the second-line treatment of patients with Wilson's disease. More recently, it has also been employed as an experimental therapeutic molecule in diabetes where it improves cardiac structure in patients with diabetic cardiomyopathy and left-ventricular hypertrophy. TETA is metabolized by acetylation, which leads to the formation of two main metabolites in humans and other mammals, monoacetyl-TETA (MAT) and diacetyl-TETA (DAT). These metabolites have been identified in the plasma and urine of healthy and diabetic subjects treated with TETA, and could themselves play a role in TETA-mediated copper chelation and restoration of physiological copper regulation in diabetes. In this regard, a potentiometric and spectrophotometric study of Cu^{II}-complex formation equilibria of TETA, MAT and DAT is presented here, to provide a comprehensive evaluation of the stoichiometries of the complexes formed and of their relative stability constants. A potentiometric study has also been conducted on the corresponding Zn^{II} complexes, to evaluate any possible interference with TETA-mediated Cu^{II} binding by this second physiological transition-metal ion, which is present in similar concentrations in human plasma and which also binds to TETA. An ESI-MS study of these systems has both confirmed the complex formation mechanisms established from the potentiometric and spectrophotometric results, and in addition provided direct information on the stoichiometry of the complexes formed in solution. These data when taken together show that the 1 : 1 complexes formed with Cu^{II} and Zn^{II} have different degrees of protonation. The stability of the Cu^{II} and Zn^{II} complexes with the three ligands, evaluated by the parameters pCu and pZn, decreases with the introduction of the acetyl groups. Nevertheless the stability of Cu^{II} complexes

with MAT is sufficiently high to enable its participation in copper scavenging from the patient. A speciation study of the behavior of TETA and MAT with Cu^{II} in the presence of Zn^{II} at physiological plasma concentrations is also presented. While Zn^{II} did not hinder copper binding, the possibility is raised that prolonged TETA treatment could possibly alter the homeostatic regulation of this essential metal ion. The lack of reliable literature stability constants concerning the Cu^{II} and Zn^{II} interaction with the major transport proteins in plasma is also briefly considered.

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