

as a function of copper supply, has revealed that several enzymes are particularly sensitive to copper deficiency and can act as an early warning signal of deficiency. These enzymes include ascorbate oxidase and diamine oxidase. Their assays have been shown to be at least as sensitive and indeed more reliable than atomic absorption analysis of copper content. In a simplified assay, ascorbate oxidase activity has been used to provide a field test that is quick, reliable and robust.



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ARGYRIOS VARSAMIDIS

GUY BERTHON

Centre de Technologie Biomédicale INSERM SC 13

Laboratoire de Chimie Bioinorganique

Université Paul Sabatier

38, rue des Trente-six ponts, 31400 Toulouse
France

MALATE AS A POTENTIAL AGENT TO PROMOTE HISTAMINE CATABOLISM

The most of the histamine present in the human body is stored in mast cells in tissues and in basophils in blood [1]. Its release from these sites may be triggered by immune reactions involving IgE antigens, or may directly result from non immunological stimuli such as the incorporation of so-called "histamine liberator" substances inside the membrane of the storage cells [1,2].

When localized, this release will lead to slight disorders like itching, redness and skin edema. When generalized, it may cause profound changes to the cardiovascular system and induce anaphylactic — or anaphylactoid, depending on the respective type of stimuli above — shock [1-3]. Concerning this, the demonstration of a close correlation between the plasma concentration of histamine and the seriousness of the symptoms

observed constituted an important breakthrough in the understanding of the physiological action of this mediator [4-6].

It has been known for a long time that histamine undergoes a rapid destruction in tissues [3]. It thus appears that increasing its rate of diffusion from blood into the environmental tissues may help alleviate its toxic effects. However, account being taken of the complexity of the system of labile equilibria characterizing the species potentially involved, it is impossible to discriminate the predominant forms under which histamine is present in blood plasma on an experimental basis.

A series of studies was thus devoted to the simulation of the distribution of histamine in this biofluid [7-11], which led to the following conclusions: (i) the most important fraction of histamine (about 99%) is constituted by its electrically charged mono- and di-protonated forms, and as such is not likely to passively diffuse through cell membranes, (ii) about 1% of histamine remains free, but its molecular form is highly polar [3], which also makes its passive diffusion unlikely, (iii) a small fraction whose percentage is inferior to 1% represents the binary and ternary metal complexes of histamine [11]. In the normal state, more than 70% of this fraction consists of the electrically neutral zinc-histamine-cysteinate complex, the majority of the remainder involving charged ternary copper complexes.

The hypothesis was thus put forward that zinc could indirectly favour histamine diffusion from plasma to tissues, hence its catabolism rate, whereas copper would in contrary exert an antagonistic effect [11]. This interpretation of the simulation results is in line with the roles previously attributed to zinc and copper in the evolution of the pharmacological effects of histamine in mice [12]. Subsequently, applications of the principles of the hypothesis above were developed using the aforementioned blood plasma simulation model [13,14]. Firstly, an attempt was made at increasing the concentration of the naturally occurring zinc-histamine-cysteinate complex by raising that of cysteine, but this proved unsuccessful [11]. A second study used aspartate and glutamate as successive partner ligands for zinc and histamine, but the increase of the neutral complexed fraction of histamine due to each of these two ligands was

almost totally compensated for by a correlative decrease in the concentration of the cysteinate ternary complex above [15].

Our latest investigation on the subject deals with the formation of ternary complexes of zinc and histamine with a series of dicarboxylic acids. Indeed, these substances are likely to meet the following requirements: (i) to have a low affinity for zinc on their own, (ii) to induce the formation of stable ternary complexes of this metal with histamine. In this respect, ligands with O donors are well known to form particularly stable mixed-ligand complexes of 3d metal ions with aromatic amines [16], especially those including an imidazole moiety [17].

Among oxalate (studied as a reference), fumarate, succinate and malate, only the latter can be expected to promote a significant increase of the neutral metal-complexed fraction of histamine in blood plasma.

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MICHEL BRION

LUC LAMBS

GUY BERTHON

Centre de Technologie Biomédicale INSERM SC 13

Laboratoire de Chimie Bioinorganique

Université Paul Sabatier

38, rue des Trente-six Ponts, 31400 Toulouse

France

DO TETRACYCLINES HAVE ANY INFLUENCE ON ZINC AND COPPER BIOAVAILABILITIES AT BLOOD THERAPEUTIC LEVELS?

Growing attention has recently been paid to the possible interference of organic pharmaceuticals with essential trace metal bioavailabilities [1-3]. Indeed, a vast majority of these substances contain donor groups likely to bind metal ions to such an extent that the normal distribution of the latter may be significantly upset. This may either lead to the expected activity of the drug or result in the occurrence of undesirable side effects [1-5]. As far as tetracyclines are concerned, their interactions with metal ions have been reported to play a critical part in important biological processes such as their deleterious impact on mineralizing tissues [6], their antibacterial activity [7] and their gastrointestinal absorption [8].

Analysing these interactions on a quantitative basis is not straightforward since, (i) account being taken of both antibiotic therapeutic doses and trace metal levels occurring *in vivo*, the concentrations of the complexes formed by tetracycline derivatives are very low, (ii) attempts at concentrating these species would upset their labile equilibria, hence their particular distribution in the biological fluid. In such cases, the only available investigation technique consists of the use of computer models which permit to simulate the distribution of all the coexisting complexes. Such models [9-11] are built up from (i) the analytically measurable overall concentrations of the reac-