Review:
Copper and inflammation – a possible rationale for the pharmalogical manipulation of inflammatory disorders

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Abstract

Acute and chronic inflammations are characterized, among other features, by changes in the metabolism of copper and by a widespread responsiveness to the therapy with copper-containing molecules.

The exact map of inflammation-induced copper movements as well as the role played by the metal in the pathogenesis of inflammatory disorders are, however, far from being clear, and this is especially true in the case of chronic processes.

Nevertheless the present knowledge suggests that the ‘copper approach’ may provide a new way for coping with the problem of anti-inflammatory/anti-arthritic therapies. The administration of exogenous copper, and the in vivo manipulation of the endogenous metal levels are proposed as two possible therapeutic strategies, not necessarily mutually exclusive.

For a better understanding of the value of such an approach, further research work is needed, especially to attain a more detailed know-how on the involved chemical forms, distribution and functions of copper in both normal as well as inflamed organisms.

Introduction

The copper content and ceruloplasmin activity of serum are known to be significantly elevated above normal values in inflammatory diseases in man and laboratory animals. Paradoxically, copper (in widely different chemical forms) is employed as a therapeutic agent for acute and chronic inflammation, in both man and animals. Taken together these observations would appear to be contradictory and brought, a few years ago, WHITEHOUSE [1] to define as ‘ambivalent’ the role played by copper in inflammation. Also BONTA [2] suggested copper is amongst the endogenous modulators of the inflammatory process.

Sometimes the word ‘modulator’ helps scientists to define the indefinable. For copper this has long been the situation since, in spite of the experimental progress one still cannot use, strictly speaking, a more precise word to define the role of endogenous copper in the cascade of events which characterizes inflammation. In 1979, following a SORENSON’s [3] previous suggestion, we proposed that the rise of total serum copper measured in inflammation could actually represent a natural anti-inflammatory response of organism; the role displayed by copper in the metabolism of connective tissue, the involvement of copper in prostaglandin biosynthesis and in free radical metabolism, together with our results on the influence of copper-deficiency on the development of the acute inflammatory process were referred to as indications speaking in favour of the proposed theory [4]. Since then this idea had been sustained by further, though certainly not conclusive, evidence which has also stimulated further research for copper-based therapies for treatment of inflammatory disorders.

The purpose of this review is to summarize recent experimental data obtained showing the involvement of endogenous copper in acute and chronic inflammatory conditions in an attempt to develop a rationale for manipulating copper levels to a therapeutic end.

Copper in chronic inflammation

(A) Therapeutic value of copper administration

Comprehensive reviews have been published recently summarizing the biochemistry and the pharmacological activities of copper in the treatment of rheumatoid arthritis and other degenerative connective tissue diseases [5], and reporting the ability of copper complexes to reduce the symptoms of chronic inflammation, especially adjuvant arthritis, in laboratory animals [5–8]. On the other hand, pulverized metallic copper and simple copper salts, like basic copper acetate and copper(II) sulphate, were used 3500 years ago for treating chronic inflammation of the eye [9]; moreover, the copper bracelet, an old anti-arthritic remedy belonging to the popular
tradition, has been recently evaluated on a scientific ground revealing to possess a potential therapeutic value which cannot be entirely neglected [10, 11]. In summary, these observations show that copper is active as an anti-inflammatory agent in chronic conditions in man and animals, and also indicate that the therapeutic effect observed may be independent of the chemical form of copper administered.

(B) Chronic inflammation in relation to copper deficiency

We found, in 1978, that copper deficiency appeared to inhibit the development of complete adjuvant arthritis in young female rats [12]. These results, later confirmed by WEST [13], were opposite to those observed in the acute inflammatory conditions [14], and we speculated that they could be explained on the basis of a lower immunocompetence of the young rats [4, 12].

Recently, KISHORE et al. [15] designed experiments aimed also to determine if the reduction in inflammation previously observed in adjuvant-challenged copper-deficient animals was an epiphenomenon of the immune system, i.e. an event secondary to an impairment of the immune function of the young rat. The results obtained showed that the copper-deficient rats were actually in a state of apparent immunosuppression as demonstrated by impaired responsiveness to the T-cell-dependent contact-sensitizing antigen oxazolone and diminished capacity to respond to the T-cell-independent antigen Type III pneumococcal polysaccharide. Nevertheless, KISHORE and co-workers did not find any inhibition in the development of the polyarthritic syndrome. The percentage of rats who developed the experimental disease was the same in both copper-deficient and control animals, although the severity of limb swelling was slightly but not statistically less in the former; moreover, the recovery from foot oedema was impaired in copper-deficient animals but not in the marginally copper-deficient rats who recovered at the same rate as did controls [15].

Though the above results are still somewhat inconclusive, RAINSFORD has recently proposed that a marginal copper deficiency in the population, possibly due to dietary and environmentally-induced perturbations in the levels of certain trace metals which influence copper ion status (such as that induced by cadmium and zinc), may be a contributory factor in the etiology of rheumatoid arthritis and related arthropathies [16]. This hypothesis is to some extent supported by the observations (a) that patients suffering from rheumatoid arthritis in its 'non-active' phase have serum copper levels which tend to be lower than normal [17], and (b) that a limited copper deficiency may occur in man, being both a result [18] and a contributory factor [19] of rheumatoid arthritis.

(C) Copper metabolism during chronic inflammatory processes

After initial contradictory reports [20–23] it is by now clear that, in rheumatoid arthritis, a statistically significant increase of total serum copper is detectable during the ‘active’ phase of the disease [24–26]. Also, parallel with these elevated serum copper levels, and highly significantly correlated to them, there are increases in plasma ceruloplasmin [24, 26] which may indicate that this disease is not characterized by a selective rise of the non-ceruloplasmin-bound fraction of copper as previously reported [20]. Moreover, copper and ceruloplasmin are present in appreciable quantities in the synovial fluids of rheumatic patients [27, 28]. Although alterations in copper status have been most extensively studied in rheumatoid arthritis, to date copper and/or ceruloplasmin concentrations in serum have also been found to be significantly enhanced in many other chronic inflammations, both in man and animals [29]. Also in the adjuvant arthritic rat increases of plasma total copper concentration and ceruloplasmin activity were measured [30], and, interestingly, the rise in serum copper precedes the appearance of any visible symptom of this experimental disease [12].

Despite this impressive evidence on copper and ceruloplasmin status in chronic inflammation, we still lack detailed information about the identity of the low molecular weight copper complexes naturally present in the non-ceruloplasmin-bound fractions of inflamed as well as normal sera [31]. Moreover, we lack specific knowledge about the overall movement of copper between the different compartments of the body during the chronic-inflammatory process. Some attempts have been made to clarify whether liver copper stores are directly involved in the changes of copper metabolism that occur during chronic inflammation. Thus KARABELAS found a dramatic increase of liver copper concentration