

Letters to the Editor

Interactions of divalent ions in nickel-sensitive subjects

Dear Sir

We read with interest the recent and valuable article by Van den Broeke et al. (1). The authors draw the conclusion that their combined in vitro and in vivo results indicate that Ca^{2+} , Cu^{2+} , Fe^{2+} , Mg^{2+} and Zn^{2+} are not able to antagonise the formation of Ni^{2+} and Co^{2+} antigens. In their paper, they quote (p. 267, lines 10–14) the conclusions reached by ourselves in a previous paper (2). However, this quotation presents misleading information. In fact, the title of this paper was "Interactions of sulfates of divalent metals in nickel-sulfate-sensitive patients" and the reported aim was "to verify whether the allergic reactions to nickel sulfate 0.1 M may be reduced or inhibited by sulfates of divalent metals other than magnesium". Moreover, our conclusions referred to the interactions between *sulfates* of nickel and *sulfates* of divalent metals *simultaneously* applied. In addition, in a following paper (3), we reported that in subjects sensitive to both nickel sulfate and nickel chloride, the simultaneous administration of aqueous solutions containing nickel chloride, mixed with molar amounts of chlorides of zinc, manganese and magnesium, was not able to inhibit positive reactions to nickel sulfate or to nickel chloride in any of the tested subjects. The conclusion drawn was that "the anion probably affects the uptake and local tissue distribution of the metal, modulating in this way, together with the individual cutaneous ligands, its effects".

The paper published by Van den Broeke et al. (1) has important implications for further understanding of the mechanism of nickel action. As stated by the authors, interactions between nickel and divalent ions occur in living systems, and are considered to be responsible for certain biological effects. In animals, the development of nickel tumors may be markedly inhibited by the simultaneous administration of one of the physiological metals, zinc, magnesium, or iron. However, the

magnitude of this inhibition is reported to be dependent on the metal, *its chemical form* and dose, and in most cases, the mode of administration (4). Thus, it is possible that even in the allergic reactions, interactions between nickel and divalent ions occur and depend upon both ions and counter ions. The authors talk about a lack of interaction between nickel chloride and chlorides of divalent metals. Although they have followed a different approach, their results are in agreement with those reported in our paper dealing with chloride interactions. In the meantime, since Van den Broeke et al. (1) performed their study using nickel chloride and chlorides of divalent metals, it is better, in our opinion, to conclude that the lack of interaction concerns the Cl^- counter ion.

Yours sincerely

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Reply

Dear Sir,

We have read with appreciation the comments of Santucci and co-workers regarding our study (1). The aim of our paper was to investigate whether other essential divalent metal ions were able to inhibit an allergic contact response to Ni^{2+} and Co^{2+} . In accordance with the studies of Santucci et al. (2), our combined results obtained with the human in vitro antigen induced lymphocyte proliferation, and the Freund's complete adjuvant test in guinea pigs indicated that the chloride salts of Ca^{2+} , Cu^{2+} , Fe^{2+} , Mg^{2+} , Mn^{2+} and Zn^{2+} were not able to inhibit the immune response induced by the chloride salts of Ni^{2+} and Co^{2+} . In their letter, Santucci and co-workers express their concerns about the way we refer to his work and in particular about the possible modulating effects of the counter ion of the applied metal salts on the allergic reactions to Ni^{2+} .

Both the chloride and sulfate salts of the metals are readily dissociated in an aqueous environment at physiological pH. Therefore, we think it is justified to talk throughout the paper about the metal ions separately, instead of the undissociated metal salts. We understand that, when quoting Santucci et al. (p. 267, lines 10–14), it would have been more appropriate to specify the sulfate counter ion. However, from a second citation in the same article (p. 272, lines 50–54), it should be clear to the reader that Santucci et al. (3) studied chloride salts as well as sulfate salts of the applied metals.

With respect to the mechanism of Ni^{2+} antigen formation, it is in our opinion unlikely that the counter ion, when dissociated from the metal ions, is able to significantly influence the formation of antigenic coordination complexes of Ni^{2+} with biomolecules in an apparent metal- (Mg^{2+} -,

Mn^{2+} -, and Zn^{2+} -, but not Cd^{2+} - and Fe^{3+} -) specific manner (3). If undissociated water-soluble salts are of any importance for the allergic reaction, would have to be studied further.

Yours sincerely

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