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High-dose dietary zinc oxide mitigates infection with transmissible gastroenteritis virus in piglets

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Abstract

Background: Zinc (Zn) supplementation has been shown to reduce the incidence of diarrhea and to protect animals from intestinal diseases, but the mechanisms of this protective effect against virus infection *in vivo* have not yet been elucidated. Transmissible gastroenteritis virus (TGEV) causes diarrhea in piglets with an age-dependent decrease of severity.

Results: We used 60 weaned piglets that were divided into three groups to evaluate the effect of different Zn levels added to a conventional diet (50 mg Zn/kg diet, Zn^{low}, control group). The other groups received the diet supplemented with ZnO at final concentrations of 150 mg Zn/kg diet (Zn^{med}), or 2,500 mg/kg diet (Zn^{high}). Oral challenge infection with TGEV was performed when the pigs had been fed for 1 week with the respective diet. Half of the piglets of each group were sacrificed at day 1 and 18 after challenge infection. Fecal consistency was improved and body weights increased in the Zn^{high} group when compared to the other groups, but no direct effect of Zn concentrations in the diet on fecal TGEV shedding and mucosal immune responses was detectable. However, in the Zn^{high} group, we found a prevention of villus atrophy and decreased caspase-3-mediated apoptosis of jejunal epithelium. Furthermore, pigs receiving high Zn diet showed a down-regulation of interferon (*IFN*)-*α*, oligoadenylate synthetase (*OAS*), Zn transporter SLC39A4 (*ZIP4*), but up-regulation of metallothionein-1 (*MT1*), as well as the Zn transporters SLC30A1 (*ZnT1*) and SLC30A5 (*ZnT5*). In addition, forskolin-induced chloride secretion and epithelial resistance were controlled at a physiological level in the Zn^{high} but not the other groups. Finally, in the Zn^{high} group, we documented an earlier and higher systemic TGEV-specific serum antibody response.

Conclusions: These results suggest that high dietary Zn could provide enhanced protection in the intestinal tract and stimulate the systemic humoral immune response against TGEV infection.

Keywords: Zinc oxide, Coronavirus, Transmissible gastroenteritis virus, Cytokine, Morphometry, Electrophysiology, Zinc transporters

Background

Several *in vitro* studies have shown that zinc (Zn) has broad-spectrum antiviral activity against a variety of viruses, such as human immunodeficiency virus, transmissible gastroenteritis virus (TGEV), equine arteritis virus, and severe acute respiratory syndrome coronavirus [1-6]. Many potential mechanisms have been suggested to explain the potential beneficial effect of Zn against virus infections. For example, Zn mediates antiviral effects through the inhibition of nidovirus RNA-dependent RNA polymerases or other proteins essential for the different phases of the viral life cycle [5,6]. In addition, Zn participates in initiating and maintaining robust immune responses, in particular cytokine production and modulation of the activity of immune cells [7]. Zn induces the production of innate interferon (IFN)-α and also immune IFN-γ, and can potentiate the antiviral action of IFN-α, but not of IFN-γ [8]. Clearance of viral infections requires cytotoxic T lymphocytes, which are also highly dependent on the presence of Zn [7]. Antibody production during both the first and an immunological memory response is disturbed by Zn deficiency [9,10], indicating that Zn is necessary for optimal results following vaccination.

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