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5. *Histamine and diverse cell types*

Inhibition of anaphylactic shock by gadolinium chloride-induced Kupffer cell blockade

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Abstract. Data in the literature concerning the role of macrophages in anaphylaxis are contradictory. In the present study, the effect of macrophage blockade induced by gadolinium chloride ($GdCl_3$) on anaphylactic shock is investigated. Our observations show that $GdCl_3$ prevents lethal anaphylactic shock in mice sensitized to ovalbumin. Gadolinium chloride given i.v. in a dose of 1 mg/100 g body weight 24 or 48 h before the elicitation of anaphylactic shock resulted in 80% survival, compared with the 43% survival in the control group. The same dose of this rare-earth metal salt also greatly reduced the mortality in mice sensitized with ovalbumin containing *Bordetella pertussis* vaccine, and similarly abrogated the symptoms of anaphylaxis, including the accumulation of serotonin and histamine in the liver. The results suggest that macrophages play an important role in mouse anaphylaxis.

In severe injuries, such as shock states, the gradual activation of liver macrophages and the excessive release of macrophage-derived destructive and immunosuppressive products may contribute to the development of "multiple organ failure" [1].

Earlier we described that rare-earth metal salts, among them gadolinium chloride ($GdCl_3$), reduced reticuloendothelial activity, and thereby selectively depress the activity of the Kupffer cells [2, 3].

Kupffer cells, the resident macrophages of the liver, have been shown to express class II antigens of the major histocompatibility complex and to have the capacities for antigen uptake and presentation *in vitro*, but their regulatory roles in the induction and expression of the immune response have not been well defined. In the present studies we investigated the effects of blockade of Kupffer cell phagocytosis by $GdCl_3$ on the course of mouse anaphylaxis and the accumulation of anaphylactic mediators (histamine and serotonin) in the liver.

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Materials and methods

Male CFLP mice (Animal House, Gödöllő, Hungary) weighing 27–30 g were injected i.p. with 100 μg ovalbumin (Koch-Licht, England) precipitated with aluminium hydroxide. In some of the experiments *Bordetella pertussis* vaccine (10^{10} organisms/animal) (Human Institute for Serological Production and Research, Budapest) was used to augment sensitization. The animals were challenged i.v. 12 days after sensitization with 100 μg of the same antigen in 0.2 ml of physiological saline. The survival rate was recorded over the next 24 h. Serotonin was measured by the spectrofluorimetric method of Shellenberger and Gordon [4] and histamine by means of the radioenzymatic method of Beaven and Horakova [5]. Histamine *N*-methyltransferase was purified from rat kidney. Kupffer cell phagocytosis blockade was induced by the method published earlier [2, 3]. Gadolinium chloride (K. and K. Laboratory, Plainview, New York) was dissolved in physiological saline and injected i.v. in a dose of 1 mg/100 g body weight.

Results were evaluated biometrically with the Student *t*-test, and the chi squared test. Analysis of variance and multiple comparisons were performed by the Scheffé procedure.

Results

Our observations show that $GdCl_3$ prevents the lethal anaphylactic shock of mice sensitized with ovalbumin. Gadolinium chloride given i.v. in a dose of 1 mg/100 g body weight 24 or 48 h before the elicitation of anaphylactic shock resulted in 90% survival, compared with the 43% survival in the control group injected only with ovalbumin on day 12 of the experiment (Fig. 1). Mice sensitized with ovalbumin containing *Bordetella pertussis* vaccine exhibited much more severe anaphylaxis (10% survival), but they too were protected by $GdCl_3$ pretreatment (80% survival).

Gadolinium chloride pretreatment also greatly reduced the symptoms of anaphylaxis, including the accumulation of histamine and serotonin in the liver. Our

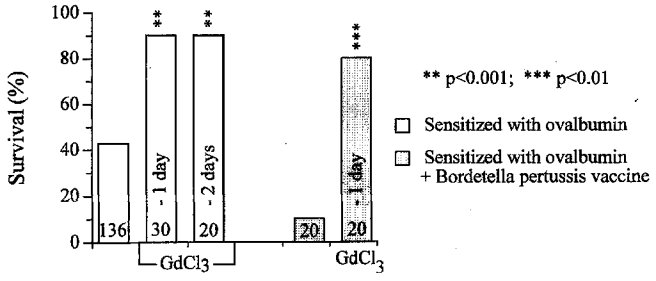

Fig. 1. Effect of gadolinium chloride on the survival rate in anaphylactic shock. Mice were sensitized with ovalbumin or ovalbumin containing *Bordetella pertussis* vaccine. Gadolinium chloride was injected in a dose of 1 mg/100 g body weight, i.v., before anaphylactic challenge on the day indicated in the figure. The numbers in the columns are the number of animals per group.

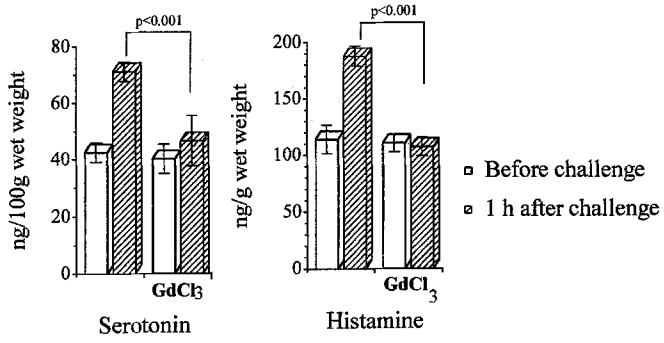

Fig. 2. Effect of gadolinium chloride on the accumulation of serotonin and histamine in the liver in anaphylactic shock. Both serotonin and histamine were determined before and 1 h after anaphylactic challenge. Mice were sensitized with ovalbumin plus *Bordetella pertussis* vaccine and gadolinium chloride was injected at a dose of 1 mg/100 g body weight, i.v., 1 day before the challenge.

observations show that the elicitation of anaphylactic shock leads to the accumulation of histamine and serotonin in the liver, but this was prevented by $GdCl_3$ pretreatment (Fig. 2).

Discussion

Rare-earth metals have diverse biological and pharmacological effects. Many of these can be explained by the replacement of calcium ion, or the inhibition of its movement across the cell membrane by these elements [3, 6]. Since the crystal radii of the rare-earth metal ions are very similar to that of the calcium ion, and because of their higher valency, they can displace and replace calcium ions in biological systems, as well as prevent the uptake of calcium ions at various cellular sites. The rare-earth metal ions markedly affect the functions of cells involved in inflammation and immunological phenomena [6]. The lanthanides inhibit the reticuloendothelial stimulation induced by zymosan, triolein and *Bacillus Callmette Guérin* (BCG) [2], chemotaxis of polymorphonuclear leukocytes, the antigen-induced histamine release from mast cells, and the proliferative response of human lymphocytes to various mitogens and to "purified protein derivative" (PPD) of tuberculin antigen [6]. According to our recent studies, $GdCl_3$ also inhibits the hypotension induced by immune globulin aggregates [7]. Hardonk et al. [8] in recent studies with the aid of Kupffer cell specific monoclonal antibodies demonstrated that $GdCl_3$ not only blocks phagocytosis of Kupffer cells, but also selectively eliminates the large macrophages situated in the periportal zone of the liver acinus. The observations that the Kupffer cell phagocytosis blockade with $GdCl_3$ greatly reduced the mortality rates and the symptoms of mouse anaphylaxis, including the accumulation of serotonin and histamine in the liver, suggest that the activation of Kupffer cells may contribute to the development of "multiple organ failure".

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