

Horse gammaglobulin-induced thrombocytopenia in anaphylaxis involving sequestration and activation of platelets

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Summary

Thrombocytopenia as well as hemoconcentration and leukopenia followed by leukocytosis were induced after HoGG challenge on HoGG-sensitized mice. Thrombocytopenia was induced within 2 min and sustained for 1 day. HoGG-induced thrombocytopenia was not observed until day 10 after sensitization; mice challenged with HoGG dose $\geq 10 \mu\text{g}$ developed thrombocytopenia. Two types of thrombocytopenia were observed in appropriately sensitized mice. HoGG induced thrombocytopenia at 2 min and 60 min, whereas, α -macroglobulin induced thrombocytopenia at 2 min, the platelet count of which returned to normal within 60 min. Poly (Glu⁶⁰Ala³⁰Tyr¹⁰) did not induce thrombocytopenia at 2 min or 60 min. The tracing study by ³H-serotonin labelled platelets demonstrated the 2 min-sequestration of platelets in lungs or livers. The HoGG-induced sequestration of platelets at 2 min was blocked by high dose heparin or Cobra Venom factor. Platelet activation at 60 min was partially inhibited by dexamethasone, rhodostomin synthetic peptide 45–59, or platelet activation factor antagonist (WEB 2086). Furthermore, the thrombocytopenia could be transferred by heat (56°C, 4 h)-treated immune sera. This suggests that HoGG-induced, non-IgE-mediated thrombocytopenia in anaphylaxis involves sequestration and activation of platelets. The sequestration in lungs occurs within 2 min and can be inhibited by high dose heparin or Cobra Venom factor. The activation of platelets involves platelet activation factor, and fibrinogen receptor.

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Introduction

Antigen-induced immune responses are evaluated by various parameters such as antibody production, delayed-type hypersensitivity, cytotoxic T cell activity, T cell proliferation, cytokine production, etc. Recently, we reported a novel type of antigen-specific hypersensitivity within 1 h of antigen challenge and referred it as early-type hypersensitivity (ETH) [1,2]. This ETH could be transferred by either immune sera or T cell-derived small molecular weight factors, and was therefore thought to be different from IgE-mediated

hypersensitivity or delayed-type hypersensitivity (DTH). The ETH was induced by most antigens tested and was also under the control of the immune response gene. The time interval required for various types of hypersensitivity to develop after immunization varied. DTH required 4–6 days, ETH required 8–11 days, while immune complex-type hypersensitivity required 18–21 days. Although ETH required 3 days more to develop compared with DTH, it lasted longer once developed, and the pattern of the response was inversely related to DTH. The ETH response involved an increased vasopermeability and oedema after subcutaneous injection of antigen in the ear. However, when the antigen was given intravenously, mice developed anaphylactic symptoms such as lethargy, tachypnoea, and myoclonic jerk. Tachy-

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cardia can also be specifically induced by antigen [3]. The present study reports on HoGG-induced thrombocytopenia in anaphylaxis in HoGG-sensitized mice.

Materials and methods

Mice

Breeders of BALB/c were purchased from The Jackson Laboratory, Bar Harbor, ME, USA. They were maintained on standard laboratory chow and water *ad libitum* in the animal facility of the Medical College, National Cheng Kung University. The animals were raised and cared for following the guidelines set up by the National Science Council of ROC. The mice (ranging from 8 to 12 weeks) were used in the experiments.

Reagents

Poly (Glu⁶⁰Ala³⁰Tyr¹⁰) (GAT), horse γ -globulin (HoGG), bovine serum albumin (BSA), lysozyme, transferrin, diphenhydramine, heparin, and indomethacin were purchased from Sigma Chemical Co., St Louis, MO, USA. Fibrinogen was purchased from KabiVitrum, Stockholm, Sweden. Meanwhile, α -macroglobulin was purchased from Boehringer Mannheim GmbH, Biochemica, Mannheim, Germany. Dexamethasone (Decadron phosphate injection) was purchased from Merck, Sharp & Dohme, International Division of Merck & Co., Inc. NJ, USA. WEB 2086 was contributed by Dr C. R. Chen (Department of Internal Medicine, College of Medicine, National Cheng-Kung University). Rhodostomin synthetic peptide 45-59 (one-letter code of its sequence: CRIPRGDMPDDRCTG) was synthesized using solid-phase technique.

Induction of anaphylaxis and determination of blood cells

Groups of five mice were injected subcutaneously at the base of the tail with 50 μ l of 20 μ g antigen in CFA [4]. Twenty days after immunization, anaphylactic responses were elicited by injecting 100 μ g of the same antigen in 100 μ l of saline intravenously. In some experiments, the mice were passively sensitized with 0.15 ml of immune sera derived from HoGG-boostered mice. One hour after injection, the mice were challenged with 100 μ g of HoGG intravenously. At different time intervals during anaphylaxis, blood was collected by cardiac puncture into EDTA tube (Monoject, Sherwood Medical, St Louis, MO, USA). Circulating platelets and leucocytes were counted using a CELL-DYN 400 Hematology analyser and CELL-DYN 100 whole blood platelet counter (Sequoia-Turner Corp., CA, USA), respectively.

In vivo complement depletion by Cobra Venom factor

Lyophilized Cobra Venom factor was prepared by DEAE-cellulose chromatography from the venom of *Naja naja kaouthia* (Sigma Chemical Co., St Louis, MO, USA) according to the procedure of Takahashi and Hayashi [5]. Active fraction eluted by 0.6 M sodium chloride in 0.01 M sodium phosphate buffer gradient was collected. Preliminary experiments were performed to determine the anti-complement activity *in vivo* of the semipurified Cobra Venom factor in mice. The mice were injected intravenously with different doses of Cobra Venom factor and the complement activity was determined 1 h after by the Mayer technique [6]. It was observed that 30 μ g of semipurified Cobra Venom factor could deplete 90% of complement activity and had no effect on the platelet count within 1–2 h. Therefore, 30 μ g of Cobra Venom factor per mouse was injected intravenously 1 h before antigen challenge in the following experiment.

³H-serotonin label of platelets

The platelets were isolated from naive BALB/c mice according to the procedure of Catalfamo and Dodds [7]. Briefly, the blood was collected with trisodium citrate (3.8%, w/v, 9:1) anticoagulant. The platelet-rich plasma was separated by centrifugation of 370 g for 5 min at room temperature. Then, the platelet rich plasma was incubated with 1 μ M ³H-5-hydroxytryptamine creatinine sulfate (NEN Research Products, Boston, MA, USA) 30 min at room temperature according to the procedure of Holmsen and Dangelmaier [8]. Practically all the radioactive serotonin has been taken up by the platelets such that very little radioactivity was left in the plasma. The labelled platelets were injected intravenously into primed mice. The mice were then challenged with 100 μ g of HoGG intravenously at various times before sacrifice so that the labelled platelets stayed in the circulation at the same period for various groups. The lung, liver, or spleen were collected and 1 ml of 1 N KOH was added overnight to dissolve the tissue.

Results

Haematological changes were monitored following HoGG challenge of HoGG-primed mice. As shown in Fig. 1a, the RBC count increased significantly 5 min after intravenous injection of HoGG; haemoconcentration was manifested. The leucocyte count decreased within 2 min, but increased after 20 min (Fig. 1b). Although the difference between the experimental group and the control at 2 min was not statistically significant because the variation of leucocyte count was high, rapid and

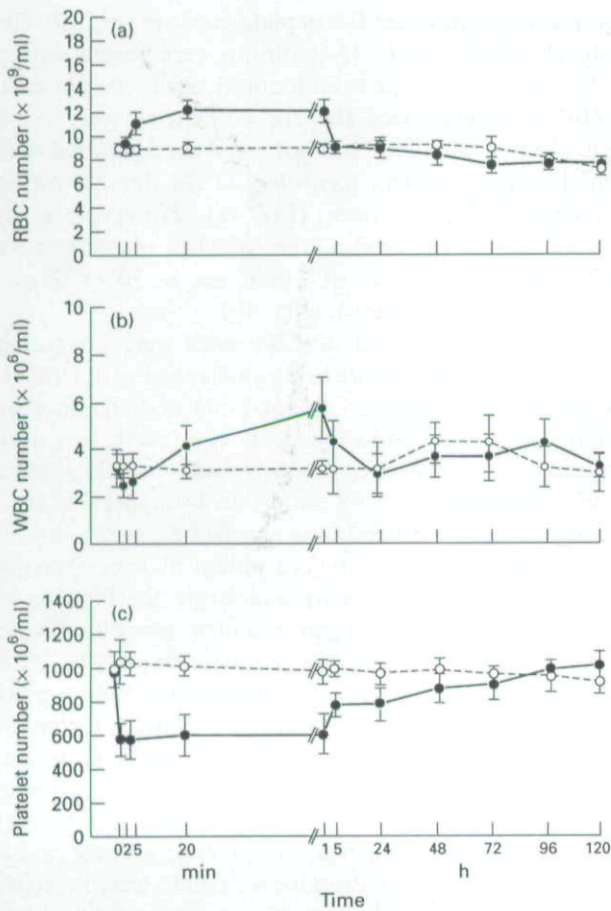


Fig. 1. Kinetics of HoGG-induced haematological changes. BALB/c mice were immunized with 20 μg of HoGG/CFA at the base of tail. Twenty days later, they were challenged with 100 μg of HoGG intravenously. Control was naive mice challenged with 100 μg of HoGG. Blood was collected at various time after challenge and (a) RBC, (b) WBC, and (c) platelet were determined as described in Materials and methods. The data of each time point were pooled from at least 20 mice. Vertical line represents the standard deviation. (a) —●—, Sensitized, - -○- -, Naive.

transient leukopenia was repeatedly observed followed by leukocytosis in anaphylaxis. The numbers of RBC and WBC returned to normal levels 5 h thereafter. The platelet count was found to decrease by 40–50% within 2 min and remained substantially lower than the control for 1 day suggesting that platelets might be activated and consumed during anaphylaxis (Fig. 1c). The characteristics of HoGG-induced thrombocytopenia were studied. Doses of HoGG as low as 10 μg could induce the HoGG-sensitized mice to develop thrombocytopenia in 2 min (Fig. 2a). The induction of thrombocytopenia was HoGG-specific since GAT would not cause thrombocytopenia in HoGG-primed mice. The

HoGG-induced thrombocytopenia could not be observed until day 10 after immunization (Fig. 2b).

Two types of thrombocytopenia were observed. HoGG induced a decrease in platelet count (> 40% drop of control) at 2 min or 60 min, whereas α_2 -macroglobulin induced thrombocytopenia only at 2 min, the platelet count of which returned to normal at 60 min. GAT did

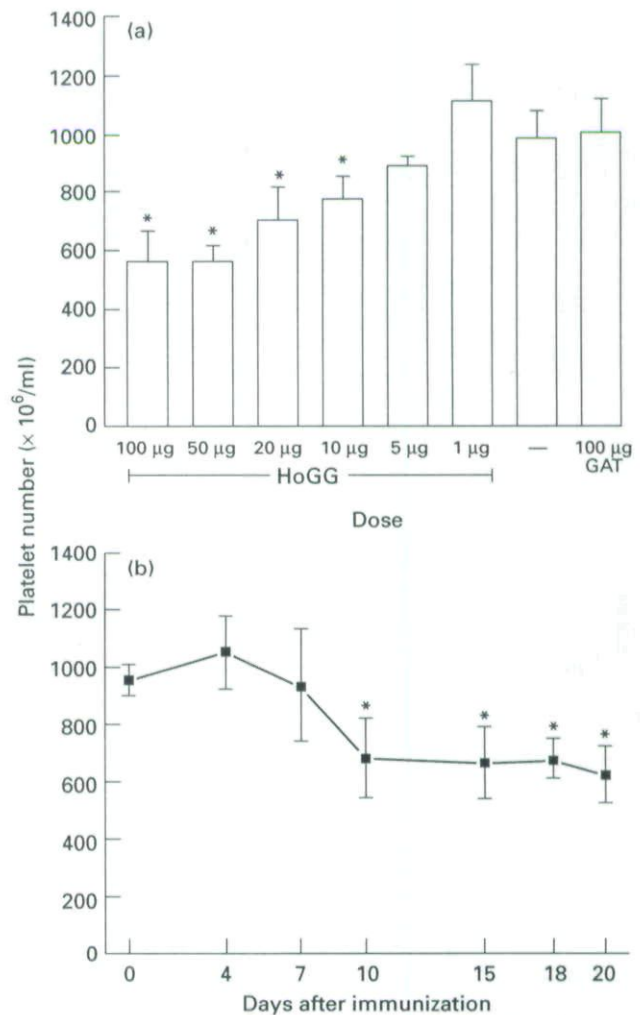
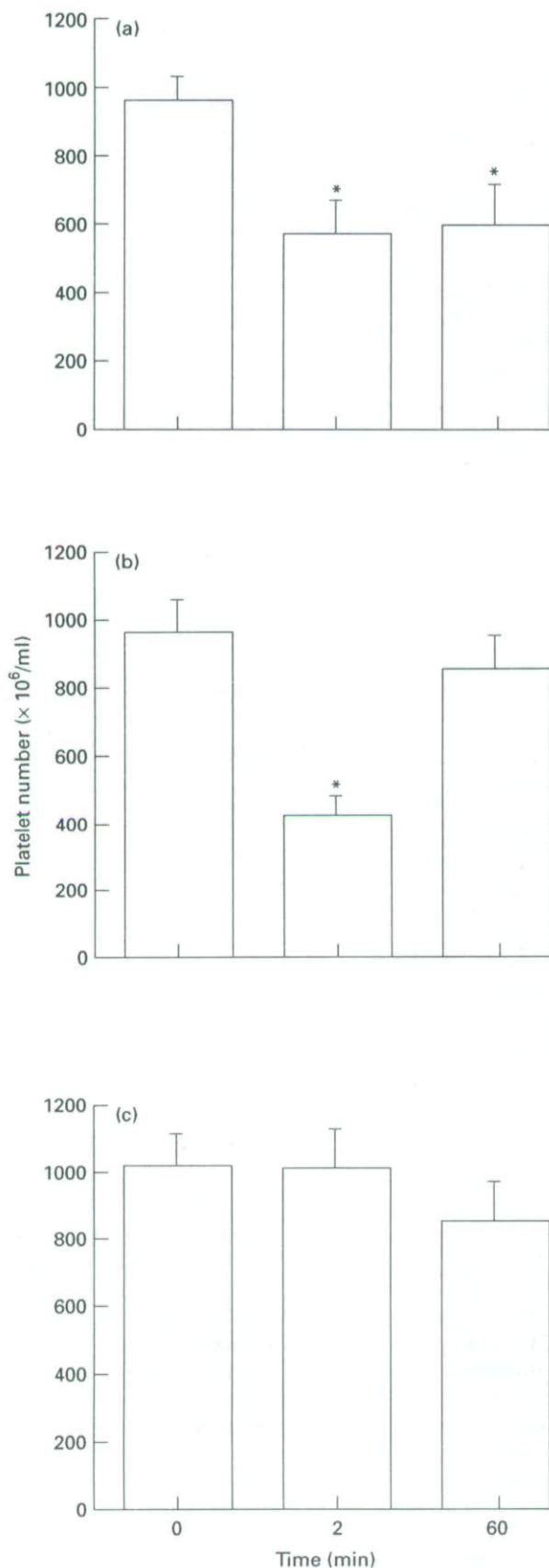


Fig. 2. Characteristics of HoGG-induced thrombocytopenia. (a) Challenging dose of HoGG. Groups of five BALB/c mice were immunized with 20 μg of HoGG/CFA at the base of the tail. Twenty days later, they were challenged with 100 μg of HoGG intravenously. (b) Kinetics of immunization. Groups of five BALB/c mice were immunized with 20 μg of HoGG/CFA at the base of tail. They were challenged at various days with 100 μg of HoGG intravenously. Blood was collected at 2 min after challenge and platelets were determined as described in Materials and methods. GAT was used as the antigen-specific control. Vertical line represents the standard deviation. * indicates that the platelet number is significant ($P < 0.01$) from non-challenged control.



not induce a significant fall in platelet count (Fig. 3). The platelets labelled with ³H-serotonin were traced during HoGG or α_2 -macroglobulin-induced thrombocytopenia. In HoGG-induced mice, the labelled platelets were found higher in lung and liver, but not in spleen compared with non-challenged control regardless of the time following challenge (2, 20, or 60 min) (Fig. 4a). However, in the case of α_2 -macroglobulin, the labelled platelets were higher in the lung only at 2 min, not at 20 or 60 min compared with the control (Fig. 4b).

The HoGG-sensitized BALB/c mice were pretreated with different drugs before being challenged with HoGG; the changes in platelet counts at 2 min and 60 min were monitored. As shown in Fig. 5, indomethacin, low dose heparin, dexamethasone, rhodostomin synthetic peptide 45-59 (rhodostomin, a 68 amino acid-polypeptide containing Arg-Gly-Asp residues, purified from the venom of *Calloselasma rhodostoma* is a potent platelet aggregation inhibitor that works by interfering the binding of fibrinogen to the fibrinogen receptor associated with GPIIb-IIIa complex on activated platelets) [9,10], WEB 2086 (PAF antagonist), or diphenhydramine had no effect on the inhibition of HoGG-induced platelet thrombocytopenia at 2 min. However, high dose heparin and Cobra Venom factor (complement depletion *in vivo*) inhibited HoGG-induced decrease in platelet count at 2 min. Furthermore, heparin, Cobra Venom factor, indomethacin, and diphenhydramine seemed to have no effect on the platelet-count drop at 60 min. In contrast, dexamethasone, rhodostomin synthetic peptide 45-59, and WEB 2086 (PAF antagonist) could block the decrease in platelet count at 60 min.

Thrombocytopenia can be transferred by immune sera; heat treatment (56°C, 4 h) did not destroy its activity (Fig. 6). Taken together, this suggests that HoGG-induced thrombocytopenia can be separated into early platelet sequestration and late platelet activation that involves PAF, and fibrinogen receptor. This thrombocytopenia is not mediated by IgE antibodies.

Fig. 3. Different patterns of thrombocytopenia induced by (a) HoGG, (b) α_2 -macroglobulin or (c) GAT. Groups of 5 BALB/c mice were immunized with 20 μ g of HoGG, α_2 -macroglobulin, or GAT in CFA at the base of the tail. Twenty days later, they were challenged with 100 μ g of the same antigen intravenously. Blood was collected at 2 min and 60 min after challenge and platelets were determined as described in Materials and methods. Vertical line represent standard deviation. * indicates that the platelet number is significant ($P < 0.01$) from non-challenged control.

Discussion

Antigen-specific systemic anaphylaxis can be induced by intravenous injection of antigen in mice sensitized by a common protocol of immunization. The mice developed

anaphylactic symptoms such as lethargy, tachypnoea, myoclonic jerk, etc. Sometimes, the mice died due to loss of effective blood volume [11]. Haematological alterations including haemoconcentration, transient leukopenia followed by leucocytosis, and thrombocytopenia were observed. Thrombocytopenia was studied further. It was found that antigen-induced thrombocytopenia in anaphylaxis can be separated into two phases: the first one is the sequestration of platelets in the lungs that occurs within 2 min after challenge and which returns to circulation 60 min afterwards. This early sequestration can be induced by HoGG or α_2 -macroglobulin, and involves complement. It could be blocked by high dose heparin or Cobra Venom factor. The second phase is the activation of platelets through PAF, and fibrinogen receptor, and is induced only by HoGG.

Antigen-specific systemic anaphylaxis has been studied in different animal models. Vargaftig *et al.* have extensively studied anaphylactic responses including bronchoconstriction, hypotension, leukopenia, and thrombocytopenia using ovalbumin as the antigen in guinea-pig or rat [12–17]. In general, the animals were sensitized with ovalbumin containing aluminum hydroxide as adjuvant, which was believed to preferentially produce IgE antibody. Histamine, peptido-leukotrienes, and platelet-activating factor were the major mediators of immediate-type, IgE-mediated hypersensitivity. Haemoconcentration, leukocytosis, and thrombocytopenia were independent phenomena associated with the presence of PAF-acether in the bloodstream. Bronchoconstriction was accompanied by a reduction of the total number of circulating platelets and leucocytes and by increased vasopermeation. Thrombocytopenia resulted from intra-vascular platelet aggregation, followed by trapping of aggregates in the microvessels, including those in the lungs. Meanwhile, neutropenia was probably accounted for by transient margination. In this study, antigen emulsified with complete Freund's adjuvant, which presumably could not generate IgE antibody, was used to sensitize mice. A high titre of antigen-specific antibodies of IgG class, but not of IgE class, was detected in sera (unpublished data). An antigen-specific hypersensitivity which did not fit into the traditional classification of hypersensitivity was reported [1]. Subcutaneous injection of antigen in the mouse ear caused increased vasopermeability at 15 min with oedema [2]. This hypersensitivity was called early-type hypersensitivity. This ETH could be transferred by heat-treated immune sera or small molecular weight T cell derived factors [1,2], and was therefore different from IgE-mediated hypersensitivity. In the system used in this study, haematological changes such as

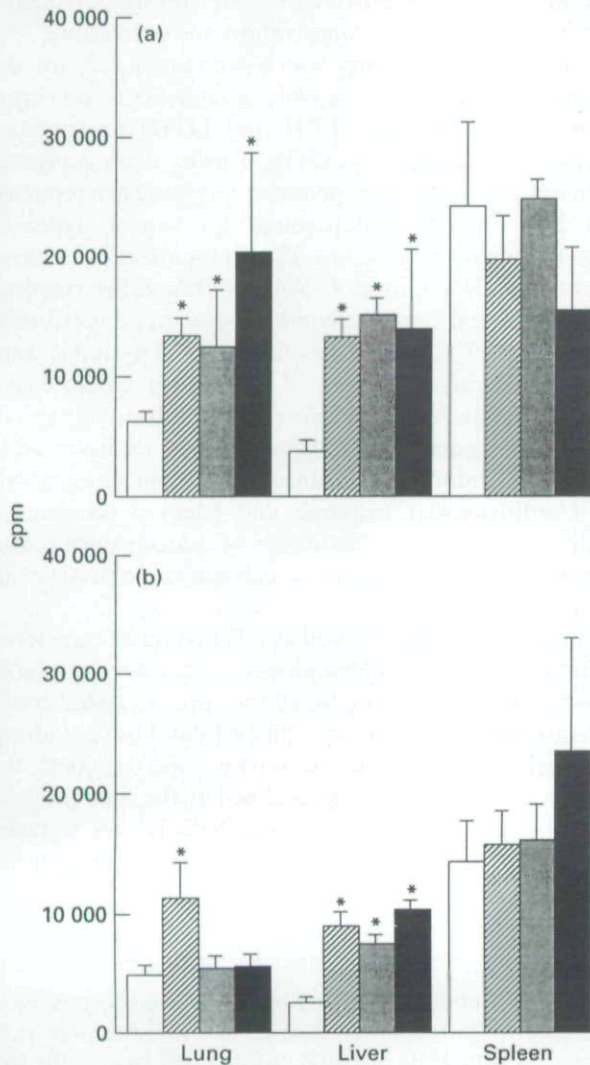


Fig. 4. Tracing of ^3H -serotonin labelled platelets in thrombocytopenia induced by HoGG or α_2 -macroglobulin. Groups of five BALB/c mice were immunized with $20\text{ }\mu\text{g}$ of HoGG/CFA or α_2 -macroglobulin/CFA at the base of tail 20 days before. Platelets from naive mice were isolated and labelled with ^3H -serotonin as described in Materials and methods. ^3H -serotonin labelled platelets were injected intravenously into primed mice. The mice were challenged with $100\text{ }\mu\text{g}$ of the same antigen intravenously at various time before sacrifice so that the labelled platelets stayed in the circulation at the same period for various groups. The lung, liver, or spleen were collected and the radioactivity was determined. Vertical line represent the standard deviation. * indicates that the platelet number is significant ($P < 0.01$) from non-challenged control. $\square$. 0 min. $\square$ (hatched). 2 min. $\square$ (grey). 20 min. $\blacksquare$. 60 min.

haemoconcentration, and transient leukopenia followed by leukocytosis were observed with antigen tested such as fibrinogen, α_2 -macroglobulin, transferrin, bovine serum albumin, GAT, lysozyme, or plasminogen (data not shown) in appropriate antigen-sensitized BALB/c mice. However, the changes in circulating platelets had

three patterns: the first type was that induced by GAT, BSA, lysozyme, or plasminogen which produced no significant changes in circulating platelets after antigen challenge; the second was transient platelet sequestration induced by α_2 -macroglobulin, fibrinogen, or transferrin; and the third was HoGG-induced thrombocytopenia that involved platelet sequestration and activation.

The types of immunity which are responsible for the thrombocytopenia of systemic anaphylaxis are intriguing. Either biphasic (ETH and DTH) or triphasic (ETH, immune-complex, DTH, if using plasma protein as an antigen) types of hypersensitivity has been reported [17]. The time interval required for various types of hypersensitivity to develop after immunization seemed to vary. DTH required 4–6 days while ETH required 8–11 days, and immune complex-type hypersensitivity, 18–21 days. The kinetic development of systemic anaphylaxis paralleled that of ETH. Haematological changes and tachycardia were observed during anaphylaxis following antigen injection. IgE was not involved in the antigen-induced tachycardia of systemic anaphylaxis [3]. Cardiovascular response and haemoconcentration might be related to dilatation of blood vessels and increased vasopermeability, which are characteristics of ETH.

Thrombocytopenia as well as ETH could be transferred by immune sera. Thrombocytopenia was also not related to immune complex because all the antigens tested could generate antibodies [18, unpublished data] but could not necessarily induce thrombocytopenia. Furthermore, the DTH response had already declined at the time (at least day 20 after immunization) anaphylaxis was induced [1,3]. Since antigen in complete Freund's adjuvant stimu-

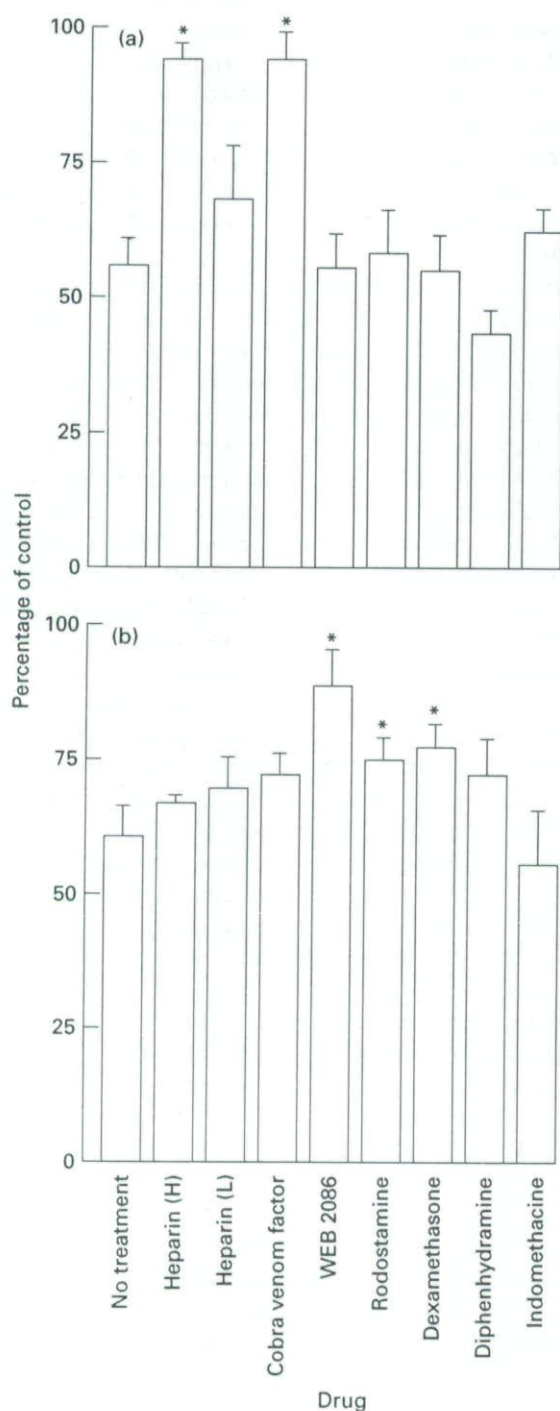


Fig. 5. Drug inhibition of HoGG-induced thrombocytopenia at (a) 2 min or (b) 60 min. Groups of five BALB/c mice were immunized with 20 μ g of HoGG/CFA at the base of the tail. Twenty days later, the mice were challenged with 100 μ g of HoGG, blood was collected at 2 min and 60 min after challenge, and platelets were determined as described in Materials and methods. Results are expressed as percentage of control value. At least three experiments were performed for each drug and vertical line represent the standard error of the mean. Mice were injected with different drugs (doses per 25 g body weight) at the indicated time before challenge (high dose heparin, 1200 IU, iv, 10 min before; low dose heparin, 350 IU, iv, 10 min; Cobra Venom factor, 30 μ g, iv, 60 min; indomethacin, 75 μ g, ip, 60 min; dexamethasone, 100 μ g, ip, 60 min; rhodostomin synthetic peptide, 500 μ g, iv, 1 min; WEB 2086, 1.5 mg, iv, 10 min; diphenhydramine, 1 mg, ip, 30 min). * indicates that the platelet number is significant ($P < 0.01$) from non-treated control subjects.

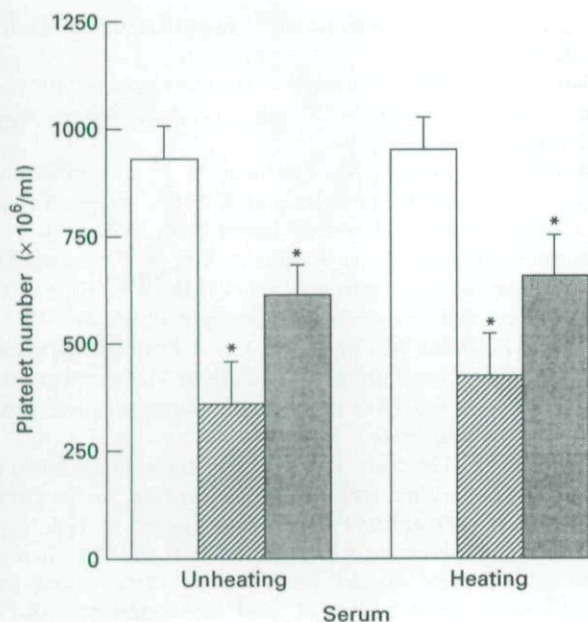


Fig. 6. Thrombocytopenia induced in serum-transfer mice. Groups of five BALB/c mice were given 0.15 ml of HoGG-boostered immune sera intravenously. One hour later, they were challenged with 100 µg of HoGG intravenously. Blood was collected before the challenge (□), at 2 min (▨), or 60 min (■) after challenge and platelets were determined as described in Materials and methods. Immune sera were heat (56°C, 4 h) treated to denature IgE antibodies. Vertical lines represent the standard deviation. * indicates that the platelet number is significant ($P < 0.01$) from non-challenged control subjects.

lates predominantly antibodies of the IgG class, rather than IgE, it is important to characterize the nature of the antigen and antibodies that are accountable for the platelet sequestration/complement activation and platelet activation, PAF, fibrinogen receptor, respectively.

Several investigators have studied antigen-induced anaphylaxis between mast cell-deficient w/w^v mice and their littermates. Jacoby *et al.* [19] found that systemic anaphylaxis could be readily induced in the mast-cell deficient w/w^v mouse, and that the anaphylactic response in this strain was clinically indistinguishable from that of the $+/+$ mouse, despite a relative lack of mast cells in the former. Ha, Reed and Crowle [20] also reported that ovalbumin-sensitized w/w^v mice could develop active systemic anaphylaxis after ovalbumin challenge. Arimura *et al.* [21,22] concluded that mast cells were not necessarily required for bovine serum albumin-induced anaphylactic shock in w/w^v mice. Munoz and Bergman [11] have reported that mice undergoing anaphylactic shock will die of circulatory failure due to loss of effective blood volume. This effective loss of volume is not only

due to dilatation of blood vessels but also to an increased permeability of the capillaries which allows fluids to escape. It was also observed that mice that experienced systemic anaphylaxis would not die if intravenously given normal saline early in anaphylaxis to supplement the blood volume (unpublished observation). Murine monoclonal antibody is widely used in clinical therapy [23,24]. The major problem encountered is the host immune response to murine immunoglobulin [25,26]. This not only causes the inefficiency of the monoclonal antibody, but also the potential side effects as reported in the literature [27–29] or as described in this study.

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