УДК 578
DOI: https://doi.org/10.17816/MAJ631424

VITRAL ASSESSMENT OF MAST CELLS DEGRANULATION MEDIATED BY IgG ANTIBODIES

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For citation: Mamontov AS, Kutukova NA, Desheva YuA, Polevshchikov AV. Vitral assessment of mast cells degranulation mediated by IgG antibodies. *Medical Academic Journal.* 2024;24(3):103–109. DOI: https://doi.org/10.17816/MAJ631424

Received: 29.04.2024 Accepted: 31.05.2024 Published online: 27.09.2024

BACKGROUND: Data on the potential for mast cell activation and degranulation under these IgG-containing immune complexes indicate the presence of another innovative pathway for mast cell activation and help explain the severe infection following vaccination.

AIM: The aim of the study was to evaluate the possibility of activation and degranulation of mast cells of peritoneal exudate in mice by binding Fcγ receptors.

MATERIALS AND METHODS: Influenza viruses A/Vietnam/1194/2004(H5N1) NIBRG-14 and A/New York/61/2015(H1N1)pdm09 were used in the work. Cells of the peritoneal exudate of CBA mice, containing an average of 7–10% mast cells, were used as a source of mast cells. The degranulation of mast cells 40 min after the introduction of IgG-containing immune complexes into cultures was assessed by the release of histamine into culture attachments. The histamine level was determined fluorimetrically after the formation of its complexes with orthophthalic aldehyde, and the histamine concentration was expressed in ng/ml.

RESULTS: In response to the binding of Fcγ receptors, a dose-dependent release of histamine from the mast cells occurs. Histamine production was noted both during the introduction of model immune complexes formed by thermally aggregated IgG, and during the formation of complexes including IgG and influenza viruses of different strains. A higher level of histamine secretion was noted during the formation of IgG complexes with the H5N1 influenza virus. The level of histamine mast cells production during Fcγ receptor binding was comparable to the response to Fcε receptor binding.

CONCLUSIONS: Binding of immune complexes containing IgG class immunoglobulins to receptors on the surface of peritoneal exudate mast cells leads to their activation and degranulation, which is accompanied by dose-dependent histamine secretion, the level of which also depends on the strain of influenza virus in the complex.

Keywords: mast cells; histamine; IgG antibodies; influenza viruses of H5N1 and H1N1 strains.

ВИТРАЛЬНАЯ ОЦЕНКА ДЕГРАНУЛЯЦИИ ТУЧНЫХ КЛЕТОК, ОПОСРЕДОВАННОЙ IgG АНТИТЕЛАМИ

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Для цитирования: Мамонтов А.С., Кутукова Н.А., Дешева Ю.А., Полевщиков А.В. Витральная оценка дегрануляции тучных клеток, опосредованной IgG антителами // Медицинский академический журнал. 2024. Т. 24. № 3. С. 103–109. DOI: https://doi.org/10.17816/MAJ631424

Рукопись получена: 29.04.2024 Рукопись одобрена: 31.05.2024 Опубликована online: 27.09.2024

Обоснование. Данные о возможности активации и дегрануляции тучных клеток под действием IgG-содержащих иммунных комплексов указывают на наличие еще одного значимого пути активации тучных клеток и позволяют объяснить тяжелое течение инфекции после вакцинации.

Цель — оценка возможности активации и дегрануляции тучных клеток перитонеального экссудата мышей при связывании Fcγ-рецепторов.

Материалы и методы. В работе использовали вирусы гриппа A/Вьетнам/1194/2004(H5N1) NIBRG-14 и A/Нью Йорк/61/2015(H1N1)pdm09. В качестве источника тучных клеток использовали клетки перитонеального экссудата мышей линии CBA, содержавшего в среднем 7–10 % тучных клеток. Дегрануляцию тучных клеток через 40 мин после внесения в культуры содержащих IgG иммунных комплексов оценивали по высвобождению гистамина в культуральные надосадки. Уровень гистамина определяли флюориметрически после формирования его комплексов с ортофталиевым альдегидом, концентрацию гистамина выражали в нг/мл.

Результаты. В ответ на связывание Fcγ-рецепторов происходит дозозависимый выброс гистамина из тучных клеток. Продукция гистамина отмечена как при внесении модельных иммунных комплексов, сформированных термоаггрегированным IgG, так и при формировании комплексов, включавших IgG и вирусы гриппа разных штаммов. Более высокий уровень секреции гистамина отмечен при формировании комплексов IgG с вирусом гриппа штамма A/H5N1. Уровень продукции гистамина тучными клетками при связывании Fcγ-рецепторов был сопоставим с ответом на связывание Fcε-рецепторов.

List of abbreviations

HAU, hemagglutinating unit; PBS, physiologic buffered saline; MC, mast cell; ADE, antibody-dependent enhancement.

Заключение. Связывание иммунных комплексов, содержащих иммуноглобулины класса IgG, с рецепторами на поверхности тучных клеток перитонеального экссудата приводит к их активации и дегрануляции, которая сопровождается дозозависимой секрецией гистамина, уровень которой также зависит от штамма вируса гриппа в составе комплекса.

Ключевые слова: тучные клетки; гистамин; IgG-антитела; вирусы гриппа штаммов H5N1 и H1N1.

Background

Mast cells (MCs) synthesize and accumulate multiple biologically active chronic inflammatory mediators and tissue remodeling factors (proteases, cytokines, growth factors, lipid mediators of inflammation) [1]. Histamine is the most widely studied and mentioned of mediators, which is secreted in large quantities by MCs upon activation by the Fcε-receptors, leading to enhanced local inflammation with vascular permeability, migration of circulating leukocytes to the site of inflammation, blood stasis, and tissue swelling that may complicate the course of the disease [2].

MCs have been reported to be involved in the pathogenesis of influenza and other viral infections [3–6]. However, the role of IgG antibodies in the antibody-dependent enhancement (ADE) of viral infections is currently being investigated [7]. The cause of ADE development is thought to be the mechanism of facilitated viral entry into cells in combination with IgG antibodies and cascade activation of the complement system [8]. Therefore, MC activation upon binding to Fcγ receptors in the context of viral infection remains the subject of many studies to date, both in influenza [9] and other viral infections [10]. As for influenza, MC degranulation levels during infection with different influenza virus strains remain poorly compared.

The aim of this study was to evaluate the possibility of activation and degranulation of mouse peritoneal exudate mast cells upon binding to Fcγ receptors.

Materials and Methods

The study used peritoneal exudate from male CBA mice weighing 16–18 g obtained from the Rappolovo husbandry (Leningrad oblast, Russia). The animals were housed in the Federal State Budgetary Scientific Institution "Institute of Experimental Medicine" (IEM) under artificial light (12/12 h) with ad libitum access to food and water. All the conditions for housing, testing, and sacrificing the animals were in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (1986) and Russian legislation (GOST 33215-2014 "Guidelines for the Care and Maintenance of Laboratory Animals" dated 01 July 2016), as well as "Rules of Laboratory Practice" of the Ministry of Health of Russia No. 708н (708n) dated 23 August 2010. Permission to work with laboratory animals in the study was obtained from the IEM local ethics committee (Conclusion # 4/19 dated 20 June 2019).

The following influenza virus strains were used, kindly provided by Professor Larsia G. Rudenko, Doctor of Medical Sciences, Professor, Honorary Scientist, Head of the Department of Virology of the IEM:

— A/Vietnam/1194/2004(H5N1) NIBRG-14 (hereinafter referred to as A/H5N1), an inactivated influenza vaccine reassortant strain obtained by reverse genetics using certified Vero cell lines,
— A/New York/61/2015(H1N1)pdm09 (hereinafter referred to as A/H1N1), an epidemic virus that has been isolated from humans without modification.

Viral particles were purified by ultracentrifugation in a step gradient of 30% to 60% sucrose. Subsequent viral manipulations were performed as previously described [11], including accumulation of viral particles, assessment of hemolytic activity, and selection of concentrations used.

Official 1% specimens of human serum γ-globulin (human anti-influenza γ-globulin, Russia) heated at 56°C for 30 minutes were used as a model of immune complexes formed by IgG antibodies. A/H5N1 virus particles complexed with mouse antibodies to this strain were also used as immune complexes. Antiviral IgG antibodies were previously shown to form and persist in serum samples [11]. Influenza A/H5N1 virus particles were incubated with antiserum to this strain of influenza virus overnight at 4°C. Serum samples containing complexes of virus particles and IgG antibodies were added to the cultures in a volume of 50 μL and incubated with cells and antibodies at 37°C for 40 minutes. Isolated A/H5N1 influenza virus particles without antibodies were introduced into the MC cultures as a control.

Mouse peritoneal exudate was used to source MCs. Exudates obtained from 7 animals after peritoneal lavage with 5 mL of physiological buffered saline (PBS) were pooled and cells were precipitated by centrifugation at 400g with cooling. After two washes with excess chilled PBS, the concentration of nuclear cells was adjusted to 2.22 mln/mL with an average MC content of 7%–10% and 200 μL were introduced to the wells of a 96-well flat-bottomed plate (Sarshtedt, Germany). Degranulation of MCs was induced by the introduction of im-

mune complexes containing virus-specific IgG and viruses of different strains at 37°C for 40 minutes. Their degranulation was evaluated by the Shore's method [12], which is based on the formation of a luminescent histamine condensation product upon interaction with 500 ng/mL orthophthalaldehyde at 355/460 nm. The fluorescence level of the specimens was measured in light-protected plates (Corning-Costar, USA) on a Thermo Scientific Fluoroskan Ascent FL Fluoroscan (USA) at 355 nm and 450 nm after mixing 200 μL of supernatant and 25 μL of ortho-phthalaldehyd solution. Results were compared based on absorbance evaluation and expressed in arbitrary units, or a parallel calibration curve was plotted using commercial histamine dilutions (MP Biomedicals, USA) instead of supernatants, with the result expressed in ng/mL.

The licensed Microsoft Excel program was used for statistical processing of the results. Statistica 6.0 software (StatSoft Inc., USA) was used to process the data obtained. Origin2019b (Origin Lab., USA) and Prism 8 (GraphPad, USA) were used to plot graphs and determine differences between independent groups.

Results

The results of histamine secretion by MCs after incubation with immune complexes containing IgG and A/H5N1 influenza virus particles and anti-IgE antibodies adsorbed on MC membrane via Fcε-receptors were evaluated (see Table 1).

Fig. 1 shows that IgE binds to membrane Fcε-receptors, resulting in the highest histamine release after binding to anti-IgE antibodies (Fig. 1, group 4). The literature reports that IgE does not bind to cellular Fcε-receptors until it binds to the antigen, and that it only acquires the ability to interact with the antigen after complexing with Fcε-receptors [13]. Histamine release also occurred in control cultures (Fig. 1, groups 0 and 1) and may be related to MC activation as a result of sample preparation. It should be noted that introduction of mouse antiserum containing anti-A/H5N1 IgG antibodies (group 1) alone did not cause any additional activation of MCs compared to the negative control (group 0). This further confirms the fact, known from the literature, that IgG molecules not bound to antigen cannot bind to Fcγ receptors on the surface of any cell. The introduction of viral particles at a dose of 50 hemagglutinating units (HAU) also did not result in high histamine release (Fig. 1, group 2). However, the introduction of viral particles complexed with IgG (group 3) resulted in a significant (compared to groups 0–2) increase in histamine release of 15%–27% compared to various controls. This result confirms both the binding of IgG molecules to membrane Fcγ-receptors only after immune complex formation and the potential for stimulation of MCs by Fcγ-receptors. However, the level of histamine secretion when signaling through Fcγ receptors was 3 times lower than when binding to Fcε-receptors (Fig. 1, group 4).

Fig. 2 shows the release of histamine by MCs after binding to IgG-containing antigen-antibody complexes using aggregated IgG as an example. Fig. 2 shows that when the concentration of aggregated immune complexes formed by heating IgG at 56°C for 30 min was changed from 0.05 μg/mL to 50 μg/mL, histamine production gradually increased, and at a complex concentration of 50 μg/mL, differences from the control be-

Table 1 / Таблица 1

Assessment of the level of histamine secretion by MCs of peritoneal exudate *in vitro* under the influence of influenza viruses of different strains and immune complexes containing them, ng/ml, *M* ± *m*, *n* = 4 for each point

Оценка уровня секреции гистамина тучными клетками перитонеального экссудата *in vitro* под влиянием вирусов гриппа разных штаммов и содержащих их иммунных комплексов, нг/мл, *M* ± *m*, *n* = 4 по каждой точке

Parameter	Influenza virus strain and dosage			
	A/H5N1		A/H1N1	
	5 HAU	50 HAU	5 HAU	50 HAU
Control (PBS)	3.26 ± 0.89		2.10 ± 0.51	
Virus	2.56 ± 0.66	2.37 ± 0.37	1.55 ± 0.27	1.47 ± 0.14
AC 1 : 300	3.76 ± 0.78	3.76 ± 0.78	3.70 ± 1.77	3.70 ± 1.77
AC 1 : 900	2.08 ± 0.33	2.08 ± 0.33	2.08 ± 0.47	2.08± 0.47
Virus + AC 1 : 300	4.12 ± 0.39	9.47 ± 0.32**	2.88 ± 0.98	1.63 ± 0.15
Virus + AC 1 : 900	3.54 ± 0.68	3.71 ± 0.25	1.54 ± 0.10	3.66 ± 1.77
Anti-IgE antibodies	10.60 ± 0.52		10.30 ± 0.35	

N o t e. AS, mouse antiserum to the corresponding influenza virus strain; PBS, physiological buffered saline; HAU, hemagglutinating Unit.

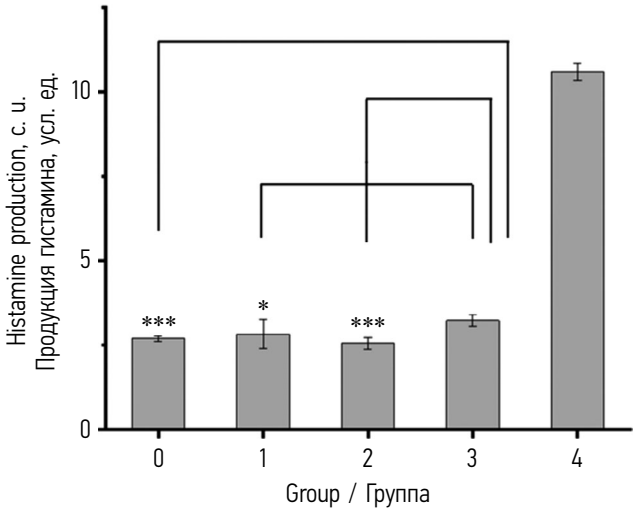

Fig. 1. Histamine secretion levels after incubation of mast cells (MC) with virus-specific IgE-containing immune complexes compared with stimulation with anti-IgE antibodies. Groups: 0, control, buffered saline solution (RFR); 1, incubation of TC with A/H5N1 virus particles; 2, incubation of MC with mouse antiserum to influenza A/H5N1 virus; 3, incubation of MC with mouse antiserum to influenza A/H5N1 virus strain and A/H5N1 virus particles; 4, incubation of MC with mouse antiserum to the influenza A/H5N1 virus, followed by the addition of antiserum to mouse IgE. The number of observations is 10 for each point. The significance of the differences was assessed for groups 0, 1, 2 compared with group 3 according to the Student's *t*-test. Here and further, the differences are significant: * at $p < 0.05$; ** at $p < 0.01$; *** at $p < 0.001$

Рис. 1. Уровни секреции гистамина после инкубации тучных клеток (ТК) с вирус-специфическими IgG-содержащими иммунными комплексами по сравнению со стимуляцией анти-IgE-антителами. Группы: 0 — контроль, забуференный физиологический раствор (ЗФР); 1 — инкубация ТК с частицами вируса A/H5N1; 2 — инкубация ТК с мышиной антисывороткой к вирусу гриппа A/H5N1; 3 — инкубация ТК с мышиной антисывороткой к вирусу гриппа штамма A/H5N1 и частицами вируса A/H5N1; 4 — инкубация ТК с мышиной антисывороткой к вирусу гриппа A/H5N1 с последующим добавлением антисыворотки к мышиному IgE. Число наблюдений 10 по каждой точке. Достоверность различий оценивали для групп 0, 1, 2 по сравнению с группой 3 по *t*-критерию Стьюдента. Здесь и далее различия достоверны: * при $p < 0{,}05$; ** при $p < 0{,}01$; *** при $p < 0{,}001$

came significant ($p < 0.05$). It should be noted that the obtained result agrees with literature data where similar results were obtained for aggregated IgG, but associated with a range of immune complex concentrations of 100–250 μg/mL [14]. It is possible that the lower threshold for reliable histamine production by the MCs resulted from the sensitivity of the Shore method used.

Significant results were obtained when comparing the level of histamine production induced by the introduction of IgG-containing immune complexes and different influenza strains such as A/H5N1 and A/H1N1 (see Table 1). Both strains were used at concentrations of 5 HAU and 50 HAU. For both strains, immune complexes were formed prior to introduction into cells. The data presented showed that at a virus dose of 5 HAE, no reliable histamine release was observed in any case compared to the negative control of PBS addition. When switching to a viral dose of 50 HAE for A/Vietnam/1194/2004 (A/H5N1) NIBRG-14 strain, a high release of histamine from MCs was reported with the formation of a circulating immune complex with a 1 : 300 dilution of the antiserum ($p < 0.01$). This release was comparable to the release of histamine induced by the introduction of anti-IgE serum.

It should be noted that for both influenza virus strains, neither the virus particles themselves nor the 1 : 300 or 1 : 900 dilutions of mouse antiviral antisera induced a release of histamine that was significantly different from the control, which is fully consistent with the results shown in Fig. 1. In addition, if immune complexes were formed by virus particles and a 1 : 300 dilution of the antiserum caused reliable histamine release, then further dilution of the antiserum to 1 : 900 eliminated the effect and the parameter did not differ from the negative control (3.71 ± 0.25 vs. 3.26 ± 0.89 in the negative control, $p > 0.05$). When a pair of influenza A/H1N1 viruses and their specific antisera were used, no reliable differences were observed compared to the negative control or to the introduction of single dilutions of antiviral antisera or immune complexes (see Table 1).

Discussion

The data show that mouse peritoneal exudate cells carry IgE antibodies on their membranes, which are associated with Fcε-receptors. Therefore, the introduction of anti-mouse IgE antibodies causes cross-linking of membrane-located IgE-FcεR complexes, resulting in histamine release by MCs without pretreatment of these cells with normal or hyperimmune antisera samples. In contrast, fixation of IgG to membrane FcγRIIIA receptors requires introduction of formed circulating immune complexes, indicating the composition of the molecular complex (virus + IgG, no any other class of immunoglobulins) that causes MC degranulation and histamine release. This is proven by data presented in the table. However, these results also suggest that not only the presence of the antigen-IgG complex is important in triggering MC degranulation, but also the properties of this antigen, e.g. the serotype of the influenza virus in our case. For example, histamine release was much lower with the A/H1N1 virus than with the A/H5N1 virus. Since there are no antigen-specific receptors on the MC membrane, only direct effects of the virus in the MC

cytoplasm can be considered, which may be mediated by cytoplasmic Toll-like receptors. Moreover, one of the mechanisms of ADE is reinterpreted; virus-IgG complex formation becomes a mechanism of virus delivery into the cell cytoplasm, bypassing any interferon-induced antiviral cell protection, and an individual set of Toll-like receptors explains the probabilistic nature of ADE syndrome [15, 16].

Additional information

Funding source. The work was carried out within the framework of research on the planned topic of the Research Institute of Experimental Medicine FGWG-2022-0005 (No. 122020300186-5) and FGWG-2022-0001 "Development of broad-spectrum drugs against mono- and mixed respiratory infections" (2022–2024).

Competing interests. The authors declare that they have no competing interests.

Author contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Personal contribution of each author: *N.A. Kutukova* — evaluation of the results of histamine secretion of MC after their incubation with immune complexes; *Yu.A. Desheva* — preparation and characterization of influenza viruses, preparation of publication; *A.S. Mamontov* — sample preparation, statistical processing of results, writing of the article; *A.V. Polevshchikov* — writing and editing of the publication.

Дополнительная информация

Источник финансирования. Работа выполнялась в рамках исследований по плановой теме НИР ФГБНУ «Институт экспериментальной медицины» FGWG-2022-0005 (№ 122020300186-5) и FGWG-2022-0001 «Разработка препаратов широкого спектра действия против моно- и смешанных респираторных инфекций» (2022–2024).

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Наибольший вклад распределен следующим образом: *Н.А. Кутукова* — оценка результатов секреции гистамина ТК после их инкубации с иммунными комплексами; *Ю.А. Дешева* — подготовка и характеристика вирусов гриппа, подготовка публикации; *А.С. Мамонтов* — пробоподготовка, статистическая обработка результатов, написание статьи; *А.В. Полевщиков* — написание и редактирование публикации.

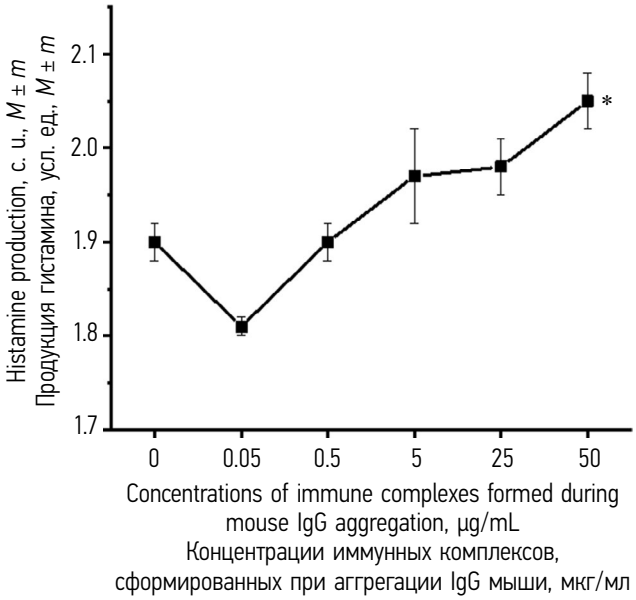

Fig. 2. Evaluation of histamine production by peritoneal exudate cells under the influence of various concentrations of aggregated IgG. The number of observations for each point is 5

Рис. 2. Оценка продукции гистамина клетками перитонеального экссудата под действием различных концентраций аггрегированного IgG. Количество наблюдений по каждой точке 5

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