İstanbul Med J 2017; 18: 109-13
DOI: 10.5152/imj.2017.74317

Review

Basophil Activation in Immediate Drug Hypersensitivity Reactions and Basophil Activation Test (BAT)

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Abstract

In the basophil activation test (BAT), the expression of the degranulation marker lysosomal-associated membrane glycoprotein-3, also termed as CD63, or upregulation of CD203c is determined. Degranulation is the fusion of specific intracellular vesicles filled with preformed mediators, which are the so-called granules, with the plasma membrane and the transition of CD63 from inside out. The result is a sudden and pronounced rise, i.e., log shift, of the fluorescence intensity signal in the detection of surface CD63 molecule. Concomitantly, the upregulation of CD203c has been observed; this can be detected as a significant increase in the mean fluorescence intensity signal of the CD203c detection antibody. The most common identification strategies use surface IgE, eotaxin CC chemokine receptor 3, the interleukin-3 receptor alpha chain CD123, the prostaglandin D2 receptor CRTH-2, or the basophil-specific ectonuclease CD203c.The usefulness of BAT in immediate drug hypersensitivity reactions is highly variable and dependent on the drug and its capacity to spontaneously conjugate to serum proteins. Stimulation with pure solutions of the parent drug or metabolites thereof versus drug-protein conjugates may influence the sensitivity and specificity of the BAT. Other influencing factors are as follows: the selection of stimulants or of identification and activation markers, the protocol for stimulation, strategies for gating, and the definition of the cut-off. The BAT is helpful to detect immediate drug hypersensitivity reactions to beta-lactam antibiotics, neuromuscular blocking agents, radiocontrast media, platinum-containing chemotherapeutics, analgesics, and biologicals or quinolone. In general, although there is a good correlation among the skin test, drug provocation test, and BAT; BAT has proven to be useful to complement in vivo tests.

Keywords: Drug, hypersensitivity, basophil, basophil activation test

Introduction

New pathways and hypotheses continue to be described in the etiopathogenesis of early drug hypersensitivity reactions (DHR) to antibiotics such as penicillin and drugs such as aspirin and nonsteroidal anti-inflammatory drug (NSAID). The best-known hypotheses are the hapten/pro-hapten and pharmacological interactions (p-i) concept (1).

Hapten/Pro-hapten concept: Small-molecular-weight drugs (hapten) and the reagent intermediates/metabolites (pro-hapten) formed after the metabolism of the drug cannot cross-link with Fcε-RI by themselves (2). In reference to the concept of hapten and pro-hapten, it is thought that basophils play a role in early developing DHRs.

P-i concept: T lymphocytes develop delayed-type immune reactions in the result of the interaction of the drugs (lidocaine, sulfamethoxazole, lamotrigine, etc.) with T cells via immunoreceptors, and basophils do not have any role here (3).

As these three hypotheses reveal, it is understood that basophils and their activation play a role in the development of early DHR. The diagnosis of early DHR is usually dependent upon the history, prick, or intradermal skin tests and the determination of the amount of specific immunoglobulin E (IgE) antibodies that develop against the drug (4). These methods are often insufficient in IgE-mediated reactions and useless in non-IgE–mediated reactions. Although drug provocation tests are accepted as the gold standard, they cannot always be performed because of ethical and practical reasons (5). Therefore, there is a need for the development of in vitro tests such as basophil activation test (BAT), which is based on the examination of cells (basophil and mast cell) involved in such allergic reactions (6).

Basophil activation test is a test showing IgE-mediated and non-IgE–mediated mast and basophil cell degranulation. Stimulation with stimulant drug or metabolite is based on the identification of basophils by flow cytometry (anti-IgE, CCR3, CRTH2, and CD203c expression, etc.) and on their activation level (through the expressions of CD63 and CD203c) (7).

This study was presented at the National Allergy and Immunology Congress, 8-12 October 2016, Muğla, Turkey.

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Received: 05.12.2016

Accepted: 27.01.2017

Even though BAT was defined about 25 years ago, it could not take its place in allergy. As it is reported in the 2016 ENDA/EAACI (European Network of Drug Allergy and Drug Allergy Interest Group of the European Academy of Allergy and Clinical Immunology) position article, if IgE-mediated/early DHR is suspected in the person, if the person is in the high-risk group, if an anaphylactic reaction has developed or in vivo skin tests cannot be performed, then in vitro tests (tests such as IgE or BAT specific to the medication) can be prioritized in this person together with the in vitro tests which have developed over time (8). In this compilation, we will dwell on the BAT method, its importance, its potential for the use in drug allergies, and its limits.

Basophil Activation Test: How is the Activation of in Vitro Basophils Provided?

Usually, whole blood, which is heparinized and anticoagulated with citrate or ethylene diamine tetraacetic acid (EDTA), is used for BAT. In order to ensure adequate degranulation, calcium must be added when the blood is put in tube with EDTA. Generally, 200 µL heparinized whole blood is compared with 200 µL buffer in negative control tube and with 200 µL anti-IgE in positive control tube for 20 min at 37°C. Sometimes anti-Fcε-RI antibodies or formyl-methionine-leucine-phenylalanine (fMLF) are used instead of anti-IgE antibodies. fMLF is an alternative degranulation/activation stimulus and is used for non-responder basophils that do not respond to in vitro IgE-mediated pathway stimulation. In the test tube, 200 µL volume of blood is compared to allergen (e.g., general anesthetic agent such as rocuronium), which is to be tested at different (minimum, maximum, and optimal) concentrations. When the allergen forms a complex with at least two specific IgE/IgE/FcεRIs, the basophil, which is in basal (calm) state, becomes active. Although the expression of CD203c partially increases (upgrade) after this activation, the expression of CD63 peaks in the result of a logarithmic increases with anaphylactic degranulation. After 20 min, the reaction is terminated with phosphate buffer solution (PBS) which is a buffer solution (containing 10 mmol/L EDTA) cooled with 1 mL of ice. The test tubes are then rotated at 4°C and 200´g for 5 min. After the tubes are prepared, in order to select the basophil and measure the activity before starting to work in flow cytometry, the cells are stained with 20 µL monoclonal anti-human IgE, 10 µL monoclonal CD63, and 10 µL CD203C antibodies on ice for 20 min (9–14). Then, the tubes are worked on in the flow cytometry.

The most common and widely used surface as a basophil identification strategy in cytometry is the IgE molecules (side scatter (SSC) ^{low} + IgE^{positive}: cell with low granulation and IgE-positive). Molecular expressions such as eotaxin CC chemokine receptor 3 (CCR3), IL-3 receptor α-chain (CD123), prostaglandin D2 receptor (CRTH-2), and basophil-specific ectonuclease CD203c are also used in the identification strategies (10). In cytometry, the expressions of CD63 and CD203c is examined as the activation markers of basophils. Sometimes, they are used together in the evaluations. It is known that the sensitivity and specificity of BAT increase when they are used together (9–14).

The expression of CD63 (LAMP-3) is a reagent that indicates cell degranulation. The granules are degranulated by combining with CD63 which is over the intracellular vesicles filled with mediator and with the plasma membrane (Figure 1), and CD63 is expressed. In this cell surface CD63 expression, a sudden and obvious increase and a log-shift (logarithmic shift) are observed in the signal of mean fluorescence intensity (MFI). Although CD203c is already expressed at the cell surface in the normal/basal state at a certain amount, after the activation, it manifests itself with a significant increase (upgrade) in the MFI signal that reflects CD203c expression (9–14; Figure 2).

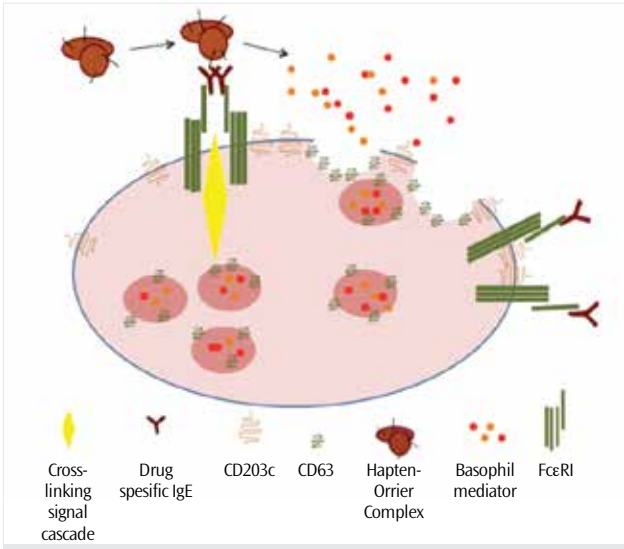

Figure 1. Schematic description of the degranulation in basophils. The mediators in the vesicles are released from the membrane as a result of the signal which occurs with the cross-linking of the hapten–carrier complex drug and the specific IgE. At this time, a logarithmic increase takes place in CD63 expression and a partial increase (upregulation) in CD203c expression (3).

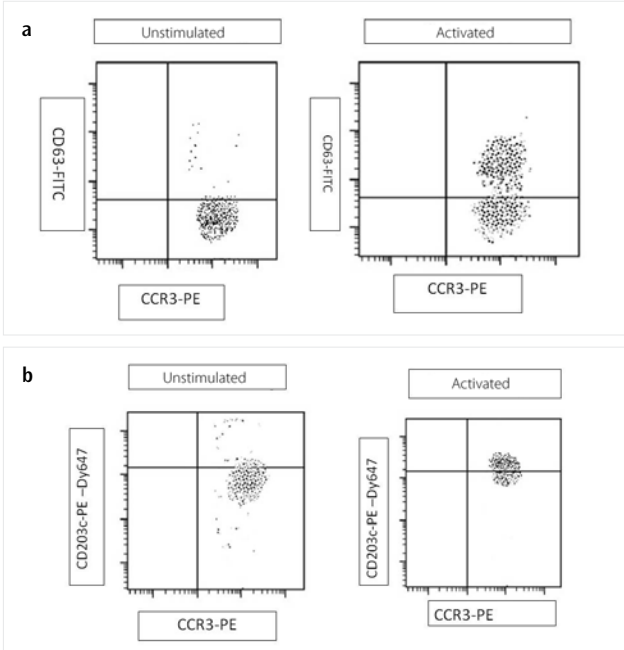

Figure 2. a,b. The demonstration of basophil degranulation in flow cytometry: (a) in comparison to non-stimulated basal basophil, a logarithmic increase in CD63 expression in activated cells and (b) a partial increase (upregulation) in CD203c expression are seen in histograms (3)

Table 1. Sensitivity and specificity of the basophil activation test

Test	Frequently used drug groups			
	antibiotics		NMBA	RCA
BAT	Beta-lactam	quinolone	Rocuronium, etc.	Radiocontrast agent
Sensitivity	%22-55	%0-100	%36-92	%46-100
Specificity	%79-100	%90-100	%90-100	%89-100
BAT	Rarely used drug groups			
	chemotherapeutics	Biological Agents	Analgesic/NSAID	
	-Platin containing-		pyrazolone	ASA
Sensitivity	%67-100	%67-100	%42-55	%17-78
Specificity	% 82-100	% 82-100	%86-100	%40-100

ASA: acetyl salicylic acid; BAT: basophil activation test; NMBA: neuromuscular blocking agent; RCA: radiocontrast agent; NSAID: non-steroidal anti-inflammatory drug

The sensitivity and specificity rates of commonly used antibiotics; neuromuscular blocking agents; radiocontrast agents; and rarely used chemotherapeutic, biological agents, and analgesic/non-steroidal anti-inflammatory drug groups are observed.

Technical Aspects of BAT Assessment

When working on flow cytometry, activation markers should be examined at minimum 200, optimal 500–1,000 basophils. The cutoff value was taken as 5% in order to spontaneously distinguish active basophils in BAT evaluation. This basal ratio needs to be subtracted from the ratio of basophils activated after the contact with allergen. Again, the severity of activation is measured through the stimulation index (SI) (%). The basophil cells that turn to CD63 /CD203C positivity with allergen compared to the negative control are measured by SI (%) or the MFI signal of the activation markers (10, 15). Again, the measurement that is called the area under the dose curve (AUC) depends on the combined assessment of basophil reactivity (maximal activation) and sensitivity (half of maximal activation). This is useful rather in the monitoring of allergen-specific immunotherapy (16–18).

The sensitivity and specificity of BAT and its availability in DHR depend on whether the stimulation is performed with the pure solutions or drug–protein conjugates of the main drug or metabolites. Other factors affecting the test include the selection of the stimulus, the stimulation protocol, the activation markers that are examined, the gating strategy, and the identification of the cutoff ratio (10, 15).

BAT in the Detection of Early DHR

In the literature, the field that was most studied with BAT is drug allergies and the b-lactam antibiotic allergies were most commonly investigated. Here, the studies with different drug groups are briefly summarized (Table 1).

Antibiotic Hypersensitivity Reactions

b-Lactam hypersensitivity

The most commonly used skin tests (prick and intradermal) have a sensitivity between 50% and 70%. BAT sensitivity is also very variable and the median is around 50% (22–55), and its specificity is between 79% and 100%. BAT and skin test results do not always overlap. The positive skin test is confirmed by BAT in 50% to 60% cases. One third of the allergic patients with negative skin test can also be detected through BAT. Although it is not superior to the skin tests, BAT is considered to be superior in detecting DHR to the drug-specific IgE immunoassay tests (8, 11). BAT also detects the cases in which drug-specific IgE cannot be demonstrated (as in the reactions of clavulanic acid which is a b-lactamase inhibitor). For these reasons, BAT is now accepted as a complementary test to skin tests (8, 11, 19).

Quinolone Hypersensitivity

Although skin tests can be used to detect DHRs developing against quinolones, false-positive reactions occur due to the skin irritation in test doses, which significantly reduces the positive predictive value of the skin test and brings it closer to random results. The photodegradation that occurs in these drugs also leads to false-negative results. For example, when BAT, which is performed to detect fluoroquinolone moxifloxacin reactions, is performed in the dark, positive results are doubled (8, 11). In a small number of studies reported in the literature, the BAT sensitivity in quinolone allergies is still very variable, and the average of the studies was found as 43% (0–100) and the specificity as 95% (90–100).

Neuromuscular Blocking Agent (NMBA) Hypersensitivity

Rocuronium, vecuronium, atracurium, *cis*-atracurium, and suxamethonium constitute 60% of the allergies. Cross-reactions are also common among them. Skin tests are considered the most reliable, and if the other tests are negative, BAT is used. In studies conducted with NMBA in the literature, the BAT sensitivity is again very variable, and the average of the studies is roughly around 62% (36–92) and the specificity is 97% (81–100) (11). In a large group of 104 patients, Leysen et al. (20) found the positive predictive value as 98% for rocuronium by using the skin test, BAT, and all the drug-specific IgE (ImmunoCAP) tests.

Radiocontrast Agent (RCA) Hypersensitivity

Skin test, provocation test, and BAT are the diagnostic methods for detecting the hypersensitivity of radiocontrast agent (RCA). In studies reported in the literature, BAT sensitivity is again very variable and the median is around 60% (46–100) and specificity is around 95% (89–100). A good correlation was found between the skin tests and drug provocation test. BAT is accepted to be a complementary test for these methods (11).

Other Drugs (Platinum-Containing Chemotherapeutic) and Hypersensitivity to Biological Agents

Although drug-specific IgEs play a role in few patients in such drug allergies, BAT is useful even in severe early DHRs, even though the

reaction is caused by pharmacological (non-IgE–mediated) mechanism (11). In studies on chemotherapeutic and biological agent hypersensitivity, which have been reported in the literature, BAT sensitivity is again very variable and the median is around 75% (67–100) and the specificity is around 90% (82–100) (11).

Analgesic/NSAID Hypersensitivity

The sensitivity of BAT used for the detection of the allergy against IgE-mediated pyrazolone was found as 42% to 55% and its specificity as 86% to 100%. When the allergy to aspirin was considered through CD63 expression, the sensitivity was 30% to 78% and the specificity was 40% to 100%; and when it was considered through CD203c expression, it was between 17% to 70% and 45% to 100%. In the cases in whom respiratory symptoms (NSAIDs exacerbated respiratory disease; NERD) occur due to NSAID–induced hypersensitivity, BAT susceptibility was found as 30% to 78%, and it was found as 37% to 100% in the cases with skin symptomatic/urticaria-angioedema (NECD and NIUA). BAT specificity was found to be 40% to 83% for NERD and 31% to 90% for those having skin symptoms (NECD and NIUA) (8).

Although used in NSAID reactions, there is uncertainty about how basophil activation occurs. Toxic concentrations of these drugs, which may lead to nonspecific responses, should not be used in tests (21). With NSAID at high concentration (5 mg/mL), basophil activation can occur even in those who tolerate certain levels of drug (8). According to the EAACI position article, the period between the reaction time and the test should be shorter than 18 months in the NSAID hypersensitivity (8). In detecting NSAID hypersensitivity, the combination of the activation marker CD203c with neither CD63 nor CAST increased the sensitivity and specificity of the test. The selection of CCR3 and CD203c combination of basophils as identifier in cytometry increases BAT sensitivity (8).

The Use in Drug-Induced Anaphylaxis in Early DHR

Kim et al. (22) reported that its use in drug-induced anaphylaxis was found to be useful and reliable. In this study, 19 patients (9 males + 10 females) with an average age of 48 and with a history of moderate/severe (five severe cases) drug-induced anaphylaxis were included in the study. The drugs causing anaphylaxis were cephalosporin, muscle relaxant, and H2 blockers. Similar to the skin tests (prick: 42%, intradermal: 58%), BAT gave a positive result in 58% of the patients. When both activation markers (CD63 and CD203c) were observed in basophils, the positivity reached 74%. According to the result of the study, it was found to be a fast-reliable test method.

The Review on the Use of BAT in Early DHR

In the review presented by Mangodt et al. (11, 12) in 2015, BAT was seen as a useful diagnostic tool in the allergies developing against NMBA, antibiotics, NSAIDs, and iodinated RCA. In drug allergies other than quinolones and NSAIDs, it was reported that the sensitivity reached 50% to 60% and the specificity reached 80% in general. It has also been emphasized that extensive collaboration is needed in order to optimize the test protocols and to demonstrate their validity in drug allergies.

ENDA/EAACI Position Article on BAT Usage

In the 2016 position article of ENDA/EAACI Drug Allergy Interest Group on the importance of in vitro tests in DHR, the literature on this subject was examined by giving examples from various studies in the literature. The level of evidence and recommendation for BAT was given as "2B" (8).

In the part of technical suggestions, although kit-based tests are commercially available, it is said that they cannot be "standardized" (8). There are differences among laboratories in terms of test protocols, reagents, procedures, and drug concentrations that are used. Since the drug-specific IgE decreases over time, the in vitro BAT test needs to be performed within three years' maximum after the reaction has occurred. It is also known that 10% of the cases are non-responders to normal test procedures, and BAT results cannot be interpreted (8).

In the part of clinical proposals; it is remarked that "BAT is recommended for the diagnosis of the reactions to beta-lactam antibiotics and NMBA and may be used as complementary to other in vitro tests." It is also said that "BAT can be recommended in the diagnosis of allergic reactions to IgE-mediated pyrazolone, fluoroquinolone, and RCAs." It is reported to have limited value due to its low specificity in the diagnosis of non-allergic NSAID hypersensitivity (8).

Alternative Method to BAT: HistaFlow

Technically, it is described as the multicolor flow cytometric measurement of the histamine release from basophil at a single-cell level through enzyme histamine, diamine oxidase (DAO) affinity method (23, 24). At the same time, HistaFlow is a method based on the analysis of histamine release in addition to activation markers. It can confirm the presence of different activation and degranulation status in basophils at single cell level. Although the Histaflow method has been developed in the last decade, its use in allergy remains limited like BAT.

Preparing the HistaFlow Technique in in-vitro environment

In addition to the BAT method described above, in order to stain intracellular histamine, after the monoclonal antibodies are placed, permeabilization and fixation of the cells are provided with 2 mL Phosflow Lyse/Fix buffer within 20 min (37°C). The cells are washed with PBS (PBS-TX) containing 0.1% Triton-X-100 and put back into suspension. Then, 10 µL of PE-labeled DAO is added, incubated at 37°C within 45 min. The cells are washed with PBS containing 0.1% sodium azide, put back into suspension and measurement is made (22). Thus, the histamine is stained with DAO conjugated with fluorochrome. Histamine release is observed in the cell before and after the activation (23–25).

Cop et al. (9) have demonstrated its safety in the reactions of IgE-mediated basophil cell developing against a drug such as rocuronium. In this study with 10 patients and 3 controls, each subject received HistaFlow test with two different doses. After the patients were exposed to rocuronium in optimal concentration, although no activation was observed in the control, CD63 expression between 11% to 86% and histamine release between 68% to 100% were observed. The flow cytometric measurement of the histamine release from basophil at single cell level has been found to be reliable with the use of Histaflow method.

Conclusion

HistaFlow method partially seems to be superior to BAT in early DHR detection in literature studies. In the near future, we think

that these complementary tests will gain the well-deserved place and importance with newly developed techniques in the diagnosis and treatment of drugs and other allergic diseases.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the author.

Financial Disclosure: The author declared that this study has received no financial support.

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Cite this article as: Özdemir Ö. Basophil activation in immediate drug hypersensitivity reactions and Basophil Activation Test (BAT). İstanbul Med J 2017; 18: 109-13.