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Responsiveness of human skin mast cells to repeated activation: an *in vitro* study

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To assess human mast-cell (MC) behavior after repetitive activation, we cocultured human foreskin MC (SMC) with human foreskin fibroblasts (F). Under these conditions, we have previously demonstrated that SMC keep their viability and functional activity for up to 8 days. SMC were presensitized with atopic serum and repeatedly activated by consecutively increasing concentrations of anti-IgE antibodies (α-IgE, 0.0002–0.1%). This treatment, which mimics the "rush desensitization" procedure, led to complete SMC unresponsiveness to activation by α-IgE at optimal concentrations, as evaluated by histamine release. However, presensitization of SMC with IgE antibodies before exposure to α-IgE restored their sensitivity to this stimulus. These data indicate that desensitization was probably due to lack of membrane-bound IgE rather than to downregulation of intracellular mechanisms. In fact, SMC challenged by an optimal concentration of α-IgE could release histamine upon a second activation by 2 h after the first activation, if the cells had been presensitized before the second challenge. SMC incubation with increasing concentrations of compound 48/80 (0.2–10 μg/ml) led to MC unresponsiveness to an optimal concentration of this stimulus. Furthermore, SMC activated by an optimal concentration of compound 48/80 and rechallenged with the same agent were insensitive to the second activation for at least 24 h. In summary, we have shown that it is possible to induce "desensitization" in SMC to both IgE-dependent and IgE-independent stimuli by incubating the cultures with consecutively increasing concentrations of the activator. SMC can release histamine when reactivated with α-IgE antibodies after presensitization by 2 h after the first challenge, while they reacquire their susceptibility to reactivation with compound 48/80 in only 2–3 days.

Key words: activation; desensitization; histamine; human skin mast cells; reactivation.

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Desensitization is a complex process that has been observed in a number of ligand-receptor systems and is defined as unresponsiveness of tissues or cells to the repetitive addition of the relevant agonist. This phenomenon can be observed *in vitro* as well as *in vivo*. "Rush desensitization" is one example of the practical use of this phenomenon in medicine. This procedure is used to desensitize allergic patients by treating them with increasing doses of antigen (1–3). While this treatment is widely used, its exact mechanism is still not clear.

Mast cells (MC) are the key cells of allergic reactions, and they are supposed to have a role in the mechanism of rush desensitization. We have previously demonstrated that in rat peritoneal MC cocultured with 3T3 fibroblasts, a temporary period of unresponsiveness to immunologic stimuli may be induced by activating the cells with gradually increasing doses of antigen (4). In addition, we have found that rat MC can be activated twice after presensitization with IgE antibodies with an IgE-dependent activator (5, 6). Similarly, rat MC challenged with compound 48/80, an IgE-independent activator, can respond to repeated activation by releasing histamine (7, 8). Recently, we have developed an *in vitro*-defined system in which human foreskin MC (SMC) are cocultured with human foreskin fibroblasts (F). Under such conditions, SMC remain viable, completely preserving their morphologic structure and functional activity for at least 8 days (9). There have been no previous investigations of the responses of human MC to reactivation and their desensitization.

In the present study, we utilized our human SMC/F coculture system to evaluate the responsiveness of human MC to reactivation with IgE-dependent and IgE-independent stimuli.

Material and methods

Human foreskin mast-cell (SMC) purification

SMC were dispersed from infant (8 days old) foreskins obtained at circumcision under sterile conditions. Samples of foreskins were put immediately in Dulbecco's modified Eagle's medium (DMEM, Biological Industries, Beit Haemek, Israel) containing 200 u/ml penicillin, 200 μg/ml streptomycin, and 1 mM EDTA (Sigma Chemicals, St Louis, MO, USA). Samples were stored at 4°C and used within 24 h.

The tissues were then chopped into fragments with scissors, and processed by enzymatic digestion, as previously described (9, 10). All manipulations were carried out under sterile conditions. SMC in the digested tissue were counted after staining with toluidine blue (0.07% in 65% ethanol, pH 3.5, Sigma), and viability was assessed by trypan blue staining (9).

Coculture of SMC with human foreskin fibroblasts (F)

F were obtained from foreskin biopsies and cultured as previously described (9). For the experiments, F were seeded in 12-well plates (Nunc, Roskilde, Denmark) in DMEM medium supplemented by 10% heat-inactivated fetal calf serum (v/v), 100 u/ml penicillin, 100 μg/ml streptomycin, and 2 mM L-glutamine ($DMEM^+$). Culture medium was changed every 2–3 days until the fibroblasts reached confluence.

Dispersed SMC (3.5×10^4/well) were seeded on confluent F monolayers. Twenty-four hours after seeding, the medium was replaced by a fresh one, to remove nonadherent cells, and experiments were started. Thereafter, culture medium was changed every 2 days.

IgE-dependent activation of SMC/F

SMC in the cocultures were passively sensitized by incubation with 10% human atopic serum (total IgE concentration 2000 u/ml from Allergy Clinic, Hadassah Hospital) in $DMEM^+$ for 2 h at 37°C. Cocultures were then washed twice with TG^{++} (Tyrode's buffer containing 0.1% gelatin, 1.8 mM $CaCl_2$, and 0.9 mM $MgCl_2$). Immunologic repetitive activation was performed at 1-h intervals by incubation of the cells for 20 min at 37°C, with gradually increasing concentrations (from 0.0002 to 0.1% in TG^{++}) of goat anti-human IgE antibodies (α-IgE, BioMakor, Rehovot, Israel). Control cultures were incubated for the first time with the same concentrations of α-IgE antibodies as the experimental cells or with TG^{++} buffer alone. At each time point, parallel cultures were terminated to determine histamine release, as described below. After the 20-min incubation, supernatants were collected from the experimental and control plates, cells were washed with $DMEM^+$ medium, and cultures were incubated at 37°C for 40 min before starting the next challenge. In the rechallenge experiments, experimental cultures were presensitized with IgE antibodies and activated as described above with α-IgE antibodies (10%). Control cultures were incubated with TG^{++} buffer alone. Cultures to be rechallenged, were washed twice with $DMEM^+$ and incubated again with IgE serum. The second activation was performed, at various time points (2 h–7 days) after the first one, with the same concentration of α-IgE antibodies used on the first one. At each time point, control cultures consisted of SMC/F challenged for the first time with the same concentration of α-IgE or with TG^{++} buffer alone. After both the first and the second activation, duplicate cultures were terminated by collecting the supernatants and scraping the cell monolayers in 0.3 ml TG^{++} with a Teflon policemen and disrupted by continuous sonication for 1 min (output 5, 50% duty cycle, Heat Systems Ultrasonics). Supernatants and cell sonicates were kept at −20°C for histamine assay.

Compound 48/80 activation of SMC/F

Repetitive activation of SMC with increasing concentrations of compound 48/80 (0.2–10 μg/ml) at 1-h intervals was essentially performed as described above for IgE-dependent activation. In the challenge and rechallenge experiments, SMC/F cultures were washed with TG^{++} and activated by incubation with 10 μg/ml of compound 48/80 for 20 min at 37°C. Cultures were rechallenged at different time points (24 h–7 days) with the same concentration of compound 48/80. Control cultures were challenged for the first time with the same concentration of compound 48/80, or just incubated with TG^{++} buffer for 20 min at 37°C. Cells and supernatants of parallel cultures were saved for histamine determination as described above.

Histamine assay

Histamine was determined in supernatants and cell sonicates by radioenzymatic assay (11). The percentage of histamine released from SMC was

calculated by dividing the amount of histamine in supernatants by the sum of that in supernatants and in cells (total).

Statistical analysis

Data are expressed as mean ± standard error (SEM). Statistical analysis was performed by Student's *t*-test. *P* values of 0.05 or less were considered significant.

Results

Repetitive challenge of SMC with increasing concentrations of α-IgE

SMC cocultured with F were presensitized with saturating concentrations of IgE antibodies and exposed to gradually increasing concentrations of α-IgE at 1-h intervals. At each time point, control cocultures underwent a single activation with the same concentration of α-IgE. Spontaneous histamine release was determined in parallel in SMC/F cocultures incubated with TG^{++} buffer alone. As shown in Table 1, a single incubation with increasing concentrations of α-IgE induced histamine release starting from 12.4±2.8% (0.001% α-IgE) and up to 66.8 ± 9.3% with the highest concentration of α-IgE (0.1%, n=3). In contrast, parallel SMC cultures, repeatedly exposed to gradually increasing amounts of α-IgE antibodies, were completely unresponsive to challenge with each concentration tested. Even when optimal concentrations of stimulus (0.02–0.1%) were added to the incubation medium, SMC released similar amounts of histamine as unstimulated, buffer-incubated, control cultures. This unresponsiveness lasted for at least 4 days. In fact, when the desensitized cells were rechallenged with the optimal concentration of α-IgE antibodies (0.1%) on day 4 after the beginning of the experiment, they released only 12.5±1.6% histamine compared to the release of 66.8±11.6% from firstly activated SMC (n=3, P<0.05).

The unresponsiveness observed in the experimental group was not due to depletion of histamine from SMC granules. In fact, SMC exposed to increasing concentrations of α-IgE still contained 20.2±4.9 ng/well histamine at the end of the procedure compared to 26.7±6.3 ng/well, at the beginning of the experiment, before challenge (n=3).

Responsiveness of SMC to rechallenge with a-IgE

In the next series of experiments, we assessed whether SMC/F activated by an optimal concentration of α-IgE antibodies can respond and release histamine when re-exposed to the same single stimulus. SMC/F were presensitized with a saturating concentration of human IgE on day 0 of the experiment and challenged with α-IgE (Fig. 1). These SMC released 48.4±8.1% of their histamine content. To determine their susceptibility to a second activation, we then presensitized SMC again with the same concentration of IgE antibodies used at time 0 at various time intervals after the first challenge. Control cocultures were presensitized with IgE on day 0 and were activated with α-IgE antibodies for the first time at each time point. As shown in Fig. 1, when SMC were rechallenged as soon as 2 h after the first activation, they released comparable percentages of histamine as control cultures (69.1±2.5 *vs* 66.2±3.9%, respectively, n=3). At the other time points (8 h–7 days), similar percentages of histamine were released from both firstly challenged and rechallenged MC. However, when SMC had not been incubated with IgE antibodies before the second challenge, they released only minute amounts of histamine, similar to those released in cultures incubated with buffer alone (5.5±2.7 *vs* 4.6±1.1, respectively), thus indicating that human SMC unresponsiveness to IgE-dependent rechallenge is probably due to lack of membrane-bound IgE. Following this observation, SMC/F cocultures which underwent repetitive challenges with increasing concentrations of α-IgE, as previously described, were incubated with IgE-rich serum before challenge with an optimal concentration of α-IgE (0.1%) 4 days after desensitization was achieved. These SMC were able to release similar percentages of histamine as cocultures activated for the first time (72.4±0.4% *vs* 66.8±11.6%, respectively).

Table 1. Repetitive challenge of human skin mast cells with increasing concentrations of α-IgE. Human foreskin MC cultured with foreskin fibroblasts were presensitized with IgE, washed, and activated at 1-h intervals (20 min, 37°C) with gradually increasing concentrations of α-IgE (α-IgE, repetitive challenge). Control cultures either were incubated with TG^{++} buffer alone or underwent single activation with α-IgE (α-IgE, single challenge). After each activation, supernatants and cells in parallel cultures were sacrificed for histamine determination. Data are mean ± SEM of three experiments performed in duplicate

	Histamine release (%)				
	Concentration of α-IgE (%)				
Stimulus	0.0002	0.001	0.004	0.02	0.1
α-IgE single challenge	8.2 ± 2.0	12.4 ± 2.8	29.0 ± 5.1	46.2 ± 10.8	66.8 ± 9.3
α-IgE repetitive challenge	8.2 ± 2.0	7.0 ± 1.1	6.7 ± 2.2	7.7 ± 1.4	6.2 ± 2.5
TG^{++} buffer	7.5 ± 2.0	5.4 ± 1.8	4.2 ± 1.8	6.3 ± 1.3	5.9 ± 2.0

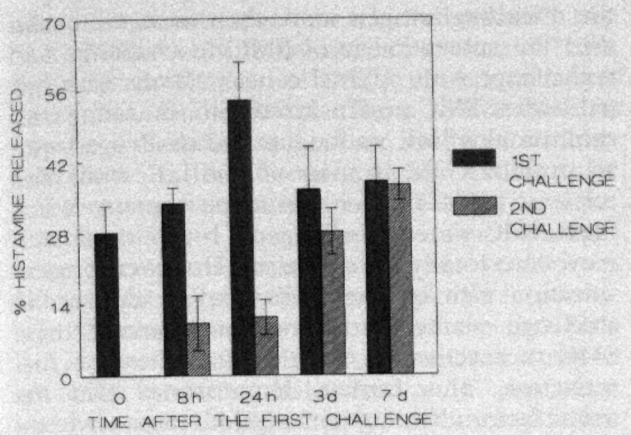

Fig. 1. Histamine released by human skin mast cells challenged and rechallenged with α-IgE. At time 0 of experiment, SMC cocultured with F were presensitized with IgE and incubated with TG^{++} buffer alone or with buffer containing 10% α-IgE antibodies (first challenge) for 20 min at 37°C. Supernatants were then collected for histamine assay, and cultures were washed and incubated with $DMEM^{+}$. At indicated time points, SMC/F which underwent activation at time 0 were again presensitized with IgE antibodies and rechallenged with α-IgE (second challenge). Cultures that were incubated with buffer at time 0 were either incubated with buffer (spontaneous histamine release) or activated for first time with α-IgE (first challenge). Spontaneous histamine release was always less than 10%. Data are mean ± SEM of 3–6 experiments performed in duplicate.

Repetitive challenge of SMC with increasing concentrations of compound 48/80

SMC/F were repeatedly challenged at 1-h intervals with increasing concentrations of compound 48/80. Control cultures were activated for the first time with the same concentrations of compound 48/80. As shown in Table 2, both experimental and control SMC cultures, when activated with 0.2–1.0 μg/ml of compound 48/80, did not release any significant percentage of histamine. Three and 10 μg/ml of this activator induced the release of 18–20% histamine in the firstly challenged control group. In contrast, repeatedly challenged SMC/F were unresponsive to these concentrations of compound 48/80, as shown by percentages of histamine released similar to those of the buffer-incubated cultures (~7%, n=3).

Responsiveness of SMC to rechallenge with compound 48/80

To assess whether SMC can respond to a second challenge with a nonimmunologic stimulator, we activated cocultures with an optimal concentration of compound 48/80 (10 μg/ml) and reactivated them with the same concentration of this activator at various time intervals (Fig. 2). Rechallenged SMC were partially unresponsive 8 h to 1 day after the first challenge. Only 3 and 7 days after activation did the cultures reacquire their full capacity to release histamine upon a second activation.

In all the different immunologic and nonimmunologic challenged and rechallenged cultures, the viability of SMC was >98% as assessed by trypan blue staining for the duration of the experiments.

Table 2. Repetitive challenge of human skin mast cells with increasing concentrations of compound 48/80. Human foreskin MC cocultured with foreskin fibroblasts were repeatedly activated at 1-h intervals (20 min, 37°C) with gradually increasing concentrations of compound 48/80 (compound 48/80, repetitive challenge). Control cultures either were incubated with TG^{++} buffer or underwent single activation with compound 48/80 (single challenge). After each activation, supernatants and cells in parallel cultures were sacrificed for histamine determination. Data are mean ± SEM of three experiments performed in duplicate

	Histamine release (%)				
	Compound 48/80 (μg/ml)				
Stimulus	0.2	0.5	1.0	3.0	10.0
Compound 48/80 single challenge	2.7 ± 1.2	9.3 ± 4.6	12.1 ± 3.7	20.3 ± 4.2	18.0 ± 2.9
Compound 48/80 repetitive challenge	2.7 ± 1.2	7.5 ± 2.0	6.0 ± 0.7	7.1 ± 0.8	9.3 ± 2.4
TG^{++} buffer	3.7 ± 1.5	10.4 ± 3.5	11.9 ± 1.7	7.2 ± 1.7	7.2 ± 1.2

Discussion

In vivo rush desensitization is a common procedure widely used to desensitize patients allergic to various drugs or bee venom (1–3, 12). In this procedure, increasing amounts of the offending antigen are administered at short intervals, resulting in desensitization and hence the opportunity to administer the compound safely. We have recently shown that it is possible to induce refractoriness in rat peritoneal MC cultures by repeated exposure to gradually increasing amounts of antigen (4). In the present report, we have extended this study to human MC. In the present study, we have shown that human foreskin MC may also become unresponsive by a similar experimental procedure. This finding confirms the key role of MC in the rush desensitization procedure in man too. The mechanism of desensitization is still not fully understood. Among possible explanations are depletion of antigen-specific IgE, sustained activation of adenylate cyclase, appearance of blocking IgG antibodies, and mediator depletion from MC and basophils (2, 13–17). In the present study, we have demonstrated that desensitized SMC still contained considerable amounts of intracellular histamine, comparable to the histamine content of SMC before activation. Thus, depletion of histamine is probably not the explanation of SMC unresponsiveness.

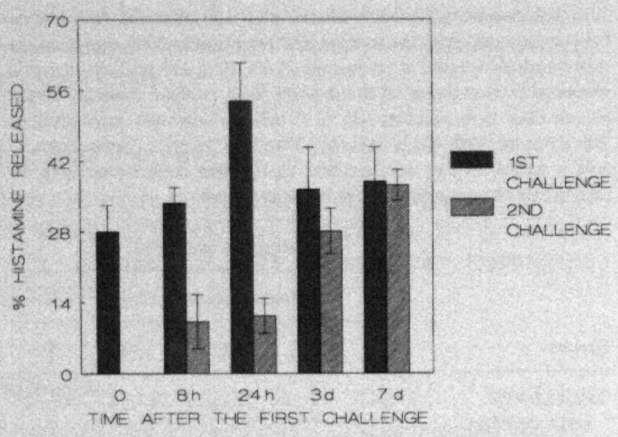

Fig. 2. Histamine released by human skin mast cells challenged and rechallenged with compound 48/80. At time 0 of experiment, SMC/F were incubated either with TG^{++} buffer alone (spontaneous histamine release) or TG^{++} buffer containing 10 μg/ml of compound 48/80 (first challenge) for 20 min at 37°C. Supernatants were then collected for histamine assay, and cultures were washed and incubated with $DMEM^{+}$. At indicated time points, SMC/F that underwent activation at time 0 were reactivated with compound 48/80 (10 μ/ml, second challenge). Cultures that were not activated at time 0 were either incubated with TG^{++} buffer alone or activated for first time with compound 48/80 (10 μg/ml, first challenge). Data are mean ± SEM of 3–9 experiments performed in duplicate.

It has been demonstrated that activation of rat basophilic leukemia cells by antigen triggers endocytosis of the cross-linked IgE with cointernalization of Fc_ε receptors occupied by monomeric IgE, causing a transient absence of IgE antibodies on the cell membrane (18). Therefore, we suggest that SMC unresponsiveness after the rush desensitization procedure is due to internalization of IgE molecules when SMC are exposed to minute amounts of antigen. The relative lack of available IgE would render the cells refractory to further stimulation even with a higher concentration of antigen. Indeed, the period of unresponsiveness lasted for at least 4 days in the absence of an exogenous source of IgE. Therefore, the reappearance of Fc_ε receptors with consequent binding of IgE antibodies when available would probably renew the responsiveness of the SMC.

The duration of the desensitization state in patients is not known. The common practice is to repeat the entire desensitization procedure if more than 24 h have elapsed from the last dose of administered allergen. This practice is reasonable since circulating allergen-specific IgE antibodies in these patients may bind to the recycled Fc_ε receptors on the MC membrane, causing desensitization and consequently susceptibility to reactivation.

In view of these observations and considering that an allergic patient is likely to be exposed to the offending antigen more than once, we evaluated the susceptibility of SMC to challenge and rechallenge with optimal concentrations of α-IgE antibodies. SMC presensitized with saturating concentrations of IgE antibodies and challenged with an optimal concentration of anti-IgE antibodies released ~50% of their histamine content. When these SMC were rechallenged 2 h to 7 days later, they were totally unresponsive. However, presensitization with IgE antibodies before the second challenge resulted in full responsiveness of these SMC to reactivation even by 2 h after the first activation. This further demonstrates that the major factor affecting human SMC responsiveness to rechallenge is associated with the availability of IgE antibodies on the cell membrane rather than lack or downregulation of intracellular biochemical events. Therefore, in allergic patients when relatively high concentrations of IgE are present, it is conceivable that skin MC will respond to a second challenge with antigen, since IgE receptors on the SMC will be quickly reoccupied.

In previous studies, we have shown that rat peritoneal MC regain their responsiveness at a slower rate (5). This difference between the two cell types may be due to the faster recycling of human IgE receptors than rat MC IgE receptors. An alternative explanation, together with the different source of the MC (human *vs* rat), is the distinct anatomic location of the two connective-tissue-type MC populations; peritoneum for rat, skin for man.

MC can also be activated by non-IgE-mediated activators. Therefore, in the second part of this study, we investigated SMC behavior after repeated activation by compound 48/80.

Rechallenge of nonimmunologic activated SMC, 8 and 24 h after the first challenge with the same activator at the same concentration, induced only a partial response. By 72 h, the cells had recovered completely and could release similar amounts of histamine as control cells activated for the first time. In addition, when SMC were incubated with increasing consecutive concentrations of compound 48/80, the cells became unresponsive to high concentrations of this substance, as observed with the similar procedure carried out with α-IgE antibodies. This shows that it is possible to induce *in vitro* rush desensitization of SMC to a non-IgE-dependent challenge as well. Therefore, in addition to classic rush desensitization to allergens, it might be possible to desensitize allergic patients also with non-IgE-dependent activators such as certain drugs.

In similar studies carried out on rat peritoneal MC activated with compound 48/80, complete responsiveness to rechallenge with the same non-

immunologic activator was achieved within 1 day (7, 8). Moreover, with the same procedure of "rush desensitization" on rat MC, unresponsiveness could not be achieved. These differences in responses of human and rat are probably attributable to the different source of MC and to their different sensitivity to compound 48/80. Therefore, it is important to stress once more that heterogeneity of responses exists in MC recovered from different species and different anatomic locations.

In summary, we have shown for the first time that *in vitro* human SMC can become refractory to activation by the "rush desensitization" procedure with both immunologic and nonimmunologic stimuli, as assessed by their incapacity to release histamine. This would indicate that MC are an important target of this procedure. Additionally, SMC can respond under the appropriate activation conditions to both IgE-dependent and -independent restimulation by releasing histamine.

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