Original articles

Tryptase and histamine release during aspirin-induced respiratory reactions

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The involvement of mast cells in the pathogenesis of aspirin (ASA)-induced respiratory reactions was investigated by measuring serum levels of tryptase, a neutral protease that is a specific marker of mast cell activation. ASA challenges were performed in 17 ASA-sensitive patients with asthma and rhinosinusitis, and tryptase and histamine levels were measured in their venous blood samples. In three subjects who experienced moderate to severe respiratory reactions extending to the skin and/or gastrointestinal tract, marked elevations of tryptase levels in postreaction serum samples (peak levels, 51.9 and 40.0 ng/ml) were discovered in two of these three subjects, and a small elevation of tryptase occurred in the serum of the third subject (3.1 ng/ml peak). Plasma histamine levels in postreaction samples were significantly elevated over baseline values in all three subjects (Δ mean plasma histamine, 238 pg/ml versus 56 pg/ml for the remaining 14 subjects; $p < 0.04$). In the remaining 14 subjects, who experienced similar respiratory reactions without extrapulmonary symptoms during aspirin challenge, changes in tryptase and histamine levels were not observed. (J ALLERGY CLIN IMMUNOL 1991;88:830-7.)

Key words: *Aspirin, aspirin-sensitive rhinosinusitis, nonsteroidal anti-inflammatory drug, FEV_1, mast cell*

Estimates of the prevalence of ASA sensitivity among adults with asthma range from 9% to 44%, depending on the method used to detect the disease and the subpopulation studied.[1-6] Currently, the mechanism of ASA-induced respiratory reactions in ASRA patients remains unknown. Histamine and leukotrienes have been detected in nasal secretions of ASRA patients during ASA-induced respiratory reactions.[7] Histamine may be released by MCs, basophils, antigen-processing cells, and possibly bacteria, whereas MCs, EOSs, neutrophils, and macrophages are capable of releasing leukotrienes.

Abbreviations used

ASA:	Aspirin
ASRA:	Aspirin-sensitive rhinosinusitis-asthmatic
MC:	Mast cell
EOS:	Eosinophil
GCRC:	General Clinical Research Center
IT:	Immunotherapy
LTB_4, LTC_4, LTD_4, LTE_4:	Leukotrienes B_4, C_4, D_4, and E_4

Tryptase, a neutral protease, is known to be the dominant protein component of the secretory granules of each of the two defined types of human MCs.[8-10] These include MC_T and MC_{TC} cells. MC_T cells contain tryptase (10 pg per lung MC_T cell), but not chymase, and are the predominate type in the lung (particularly in alveoli) and intestinal mucosa. MC_{TC} cells contain both neutral proteases (35 pg of tryptase and 4.5 pg of chymase per skin MC_{TC} cell) and are the predominate type of MC in the skin and intestinal submucosa. Tryptase is present in all metachromatic MCs of the

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Supported by General Clinical Research Center Grant No. M01RR00833 of Scripps Clinic and Research Foundation, National Institutes of Health Grant AI-20487, and Pharmacia Grant 87-0697.

Received for publication Jan. 15, 1991.

Revised May 10, 1991.

Accepted for publication May 10, 1991.

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Publication No. 6464-MEM from the Research Institute of Scripps Clinic, La Jolla, Calif.

1/1/31690

TABLE I. Single-blind 3-day oral ASA challenge*

Time	Day 1	Day 2	Day 3
8 AM	Placebo	ASA, 3 or 30 mg	ASA, 150 mg
11 AM	Placebo	ASA, 60 mg	ASA, 325 mg
2 PM	Placebo	ASA, 100 mg	ASA, 650 mg

*Individualized by the physician both with respect to incremental increase in ASA dosage and timing of administration.
From Stevenson DD, Mathison DA. Postgrad Med 1985;78:11.

TABLE II. Respiratory tract reactions that occur during ASA and NSAID challenges

Classification	Reaction
Classic	More than 20% decrease in FEV_1 values combined with nasoocular reaction
Pure asthma	A 20% decline in FEV_1 values
Pure rhinitis	Nasoocular reaction alone
Partial asthma	FEV_1 values decline by 15% to 20%, combined with a nasoocular reaction
No reaction	No evidence for reaction

NSAID, Nonsteroidal anti-inflammatory drug.
From Stevenson DD, Simon RA. Aspirin sensitivity: respiratory and cutaneous manifestations. In Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, eds. Allergy: principles and practice. 3rd ed. St. Louis: CV Mosby, 1988:1542.

skin, lung, and bowel tissue. Although tryptase is present in negligible amounts in human basophils (0.04 pg per basophil),[11] it has not been detected at all in other types of cells in the peripheral blood, skin, lung, and bowel. Thus, tryptase levels in serum can serve to specifically indicate that MC activation has occurred.[12] Levels of serum tryptase >5 ng/ml are typically found from 1 to 4 hours after the onset of systemic anaphylaxis.[12] Normal levels are <1 ng/ml (unpublished data), whereas less severe allergic reactions or samples collected more than 4 hours after the onset of symptoms may be associated with levels from 1 to 5 ng/ml.

Because most ASRA patients must take maintenance systemic corticosteroids, the potential effect of corticosteroids on MC function is important. In vitro studies of human airway MCs, pretreated with or without dexamethasone, did not reveal any differences in mediator release.[13] Thus, despite the use of corticosteroids in our study population, we would not expect these drugs to influence the results of this study.

Recently, a patient was reported who presented with severe asthma and vomiting 30 minutes after ingestion of 75 mg of indomethacin. Tryptase serum levels were markedly elevated in this patient during his reaction and declined with a halftime of 1½ hours.[14] Another patient reportedly developed bronchospasm and urticaria 1 hour after ingestion of 650 mg of ASA. Appreciably elevated tryptase levels were also detected in this patient.[12]

In an effort to understand better the mechanism of ASA-induced reactions, we undertook a study to determine whether MC activation occurred in ASRA patients during oral ASA challenges.

MATERIAL AND METHODS

Patients

All patients were adults with known reversible obstructive airway disease and rhinosinusitis/nasal polyposis. Previous and current histories of allergic respiratory tract disease, previous cutaneous tests for immediate hypersensitivity reactions, and treatment with IT were recorded. All patients had histories of lower respiratory tract reactions (wheezing, dyspnea, and chest tightness) after ASA or nonsteroid anti-inflammatory drug ingestion; some patients also observed concomitant nasoocular symptoms (rhinorrhea, nasal obstruction, postnasal drainage, and ocular irritation/watering) during their previous ASA-induced reactions. Sensitivity to ASA was documented by oral ASA challenges (a positive reaction being a prerequisite for participation in the study).[15] Informed consent for procedures approved by the Human Subjects' Committee was obtained for each patient.

Challenge procedure

Seventeen ASRA patients underwent single-blind oral ASA challenges in the GCRC at Scripps Clinic and Research Foundation. Challenges were performed at a time when the patient's asthma was in relative remission; that is, FEV_1 values were at least 70% of predicted or of the best previously recorded, with an absolute value >1.5 L. If additional corticosteroids were needed, they were administered in the week preceding challenge to induce remission in asthma. Theophylline treatment was continued, but antihistamines, cromolyn, and inhaled sympathomimetic agents were stopped 24 hours before challenge because these drugs have been demonstrated to modify rhinitic or bronchospastic responses to ASA.[15] The dosing protocol for the single-blind, 3-day oral ASA challenges is summarized in Table I. A detailed description of the challenge procedure has been described elsewhere.[15] Patients are not told about the contents of opaque capsules nor the challenge sequence during their stay in the GCRC.

Clinical reactions to ASA

The classification of respiratory reactions that occur during ASA challenges is outlined in Table II. During the challenge procedure, blood pressure and pulse rate were recorded, and cutaneous and gastrointestinal reactions were also noted as they occurred. Nasoocular signs and symptoms

TABLE III. Results of oral ASA challenges in 17 patients: Respiratory and systemic reactions

Patient	ASA-provoking dose (mg)	Respiratory reaction type	Maximal % decline in FEV_1	Maximal nasoocular sign/symptom grade	Gastrointestinal sign/symptom	Cutaneous sign/symptom
R. M.	100	Classic	31	4+	Nausea	—
S. G.	100	Classic	58	4+	Diarrhea	Severe flushing
G. R.	60	Classic	44	3+	Bloating/abdominal distension colic	Macular rash
K. W.	60	Classic	28	3+	—	—
M. D.	60	Pure asthma	35	—	—	—
N. C.	150	Pure asthma	23	—	—	—
R. L.	60	Pure asthma	26	—	—	—
D. K.	30	Classic	30	2+	—	Mild flushing
H. G.	60	Classic	28	2+	—	—
D. I.	60	Classic	20	2+	—	—
T. H.	60	Classic	37	1+	—	—
W. F.	60	Pure asthma	23	—	—	—
R. S.	60	Classic	21	2+	—	—
P. M.	6	Pure asthma	31	—	—	—
R. A.	60	Classic	28	3+	—	—
P. P.	60	Classic	33	2+	—	—
S. S.	60	Classic	58	2+	—	—

were graded on an intensity scale of 1+ to 4+ with 1+ representing minimal to mild and 4+ representing severe nasal/ocular reactions. Information about the presence or absence of extrapulmonary manifestations of the ASA reaction was not made known to the laboratory conducting the assays.

Tryptase assay

Venous serum samples were collected at baseline (before ASA challenge), 30, 60, 120, and 300 minutes after onset of clinical reaction (as defined by a 20% decline in FEV_1 values from baseline with or without concomitant nasoocular signs/symptoms). An additional serum sample was obtained at the end of the ASA desensitization protocol 3 hours after the patient ingested 650 mg of ASA without adverse effects. Samples were stored at −70° C. All sera were assayed for tryptase with a sandwich ELISA assay described elsewhere.[16] The lower limit of sensitivity with 40 μl of serum per assay was 2.5 ng/ml. Currently, levels >5 ng/ml are considered to be elevated and reflect excessive MC degranulation. Levels between 2.5 and 5 ng/ml may also occur with mild or local MC discharge or reflect early or late timing of blood sampling relative to onset of MC discharge.

Histamine assay

Venous plasma samples were collected in ethylenediaminetetraacetic acid tubes at baseline, the time of recognized clinical reaction, and at the end of the desensitization protocol, 3 hours after ingesting ASA, 650 mg. Samples were stored at −70° C before assay. Plasma was assayed for histamine by radioimmunoassay (AMAC, Inc., Westbrook, Maine). The lower limit of sensitivity with 100 μl of plasma per assay was 20 pg/ml.

Statistical analysis

Analysis of histamine values was performed with an independent Student's *t* test; *t* test, Wilcoxon's signed-rank test, and regression analysis were used to understand further the results of subgroups of ASA reactors.

RESULTS

Patients' profiles

Of the 17 patients, 10 had a history of IgE-mediated rhinitis or asthma as well as positive wheal-and-flare cutaneous test, but only 3 patients were currently judged to have active allergic respiratory disease. Seven of the 10 patients had received IT in the past, but only two were continuing this treatment at the time of study. With respect to interpretation of Tables III and IV, of the three subjects who were found to have elevated serum tryptase levels, patients R. M. and G. R. had previous allergic respiratory disease, and R. M. had received IT in the past. Patient S. G. had negative wheal-and-flare cutaneous testing in the past. All three patients were taking systemic corti-

TABLE IV. Results of histamine and tryptase levels before, at reaction, and after ASA desensitization

Patient	Plasma histamine (pg/ml)			Serum tryptase (ng/ml)		
	ASA challenges		After ASA desensitization*	ASA challenges		After ASA desensitization*
	Before	Raction		Before	Peak†	
R. M.	100	514	171	<2.5	51.9	<2.5
S. G.	86	266	42	<2.5	40.0	<2.5
G. R.	127	247	183	<2.5	3.1	<2.5
K. W.	48	78	120	<2.5	2.5	<2.5
M. D.	78	81	72	<2.5	<2.5	<2.5
N. C.	44	52	71	<2.5	<2.5	<2.5
R. L.	102	116	41	<2.5	<2.5	<2.5
D. K.	43	139	43	<2.5	<2.5	<2.5
H. G.	100	82	268	<2.5	2.5	<2.5
D. L.	38	56	38	<2.5	<2.5	<2.5
T. H.	51	40	39	<2.5	2.5	<2.5
W. F.	77	37	76	<2.5	2.5	<2.5
R. S.	114	96	543	<2.5	2.5	<2.5
P. M.	72	50	36	<2.5	<2.5	<2.5
R. A.	75	142	ND	<2.5	<2.5	<2.5
P. P.	50	94	77	<2.5	<2.5	<2.5
S. S.	93	49	53	<2.5	<2.5	<2.5

*Blood sample taken 3 hours after ingesting ASA, 650 ng, without any measurable clinical reaction.
†Peak level of tryptase is the highest value recorded between 30- 300-minute $\bar{p}$ reaction.

costeroids and theophylline at the time of ASA challenge and study. Of the remaining 14 patients, 10 were taking systemic corticosteroids.

Clinical reactions to ASA

As presented in Table III, all ASRA patients undergoing ASA challenges met criteria for an ASA-induced asthmatic reaction. Twelve patients had classic responses consisting of a decline in FEV_1 >20% from baseline with concomitant nasoocular signs and symptoms (rhinorrhea, nasal blockage, postnasal drainage, and conjunctival injection). Five patients had an asthmatic response without a nasoocular component. Hypotensive reactions, as defined by a drop in systolic blood pressure to <90 mm Hg, did not occur in any of the patients.

Also depicted in Table III are the distinguishing features of the ASA-induced reactions exhibited by R. M. and S. G. These two patients had reactions characterized by moderate and large declines in FEV_1 values (31% and 58% for R. M. and S. G., respectively) and severe (4+) nasoocular signs and symptoms; in addition, there was progression to involve the gastrointestinal tract with one patient (R. M.) experiencing significant nausea lasting 2 hours and the other patient (S. G.) having watery diarrhea and severe cutaneous flushing lasting for 90 minutes. Both patients' ASA-provoking doses were 100 mg; all other subjects except N. C. had ASA-provoking doses ≤60 mg. After ASA challenge with 60 mg of ASA, patient G. R. had a substantial asthmatic reaction with a decline in FEV_1 of 44% in addition to a moderate (3+) nasoocular reaction. The patient also experienced abdominal cramping and a macular rash. None of the other 14 patients in this study had gastrointestinal signs or symptoms, and only one patient (D. K.) experienced a transient cutaneous flush during their reaction.

Serum tryptase levels

Of the patients with classic responses to ASA challenge, two patients (R. M. and S. G.) were found to have marked elevations in serum tryptase levels during their reactions compared to baseline values. One patient (G. R.) with a classic respiratory reaction to ASA and associated gastrointestinal and cutaneous reactions demonstrated a small rise in serum tryptase to a level of 3.1 ng/ml. As presented in Table IV, five of the remaining 14 subjects appeared to have a rise in serum tryptase levels to the lower limits of detec-

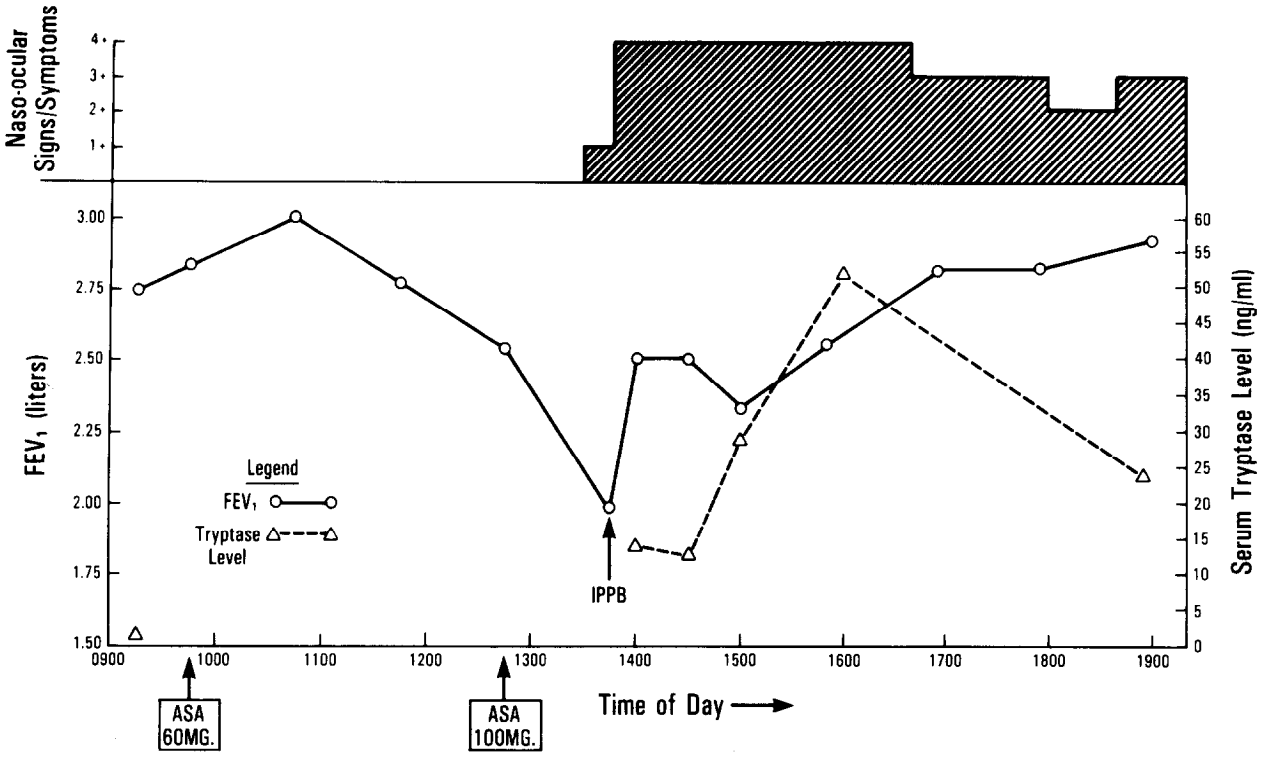

FIG. 1. In subject R. M., ASA-reaction onset occurred between 1330 to 1350 hours with a nasoocular reaction, followed quickly by a bronchospastic response. (FEV_1 decreased 31%.) Marked tryptase release, peak level, 51.9 ng/ml; this subject also experienced gastrointestinal symptoms (nausea) between 1400 and 1600 hours.

tion, 2.5 ng/ml. Samples from the remaining nine subjects did not change from the baseline values of <2.5 ng/ml.

In Fig. 1 is depicted the sequence of R. M.'s reaction and the accompanying elevation of serum tryptase levels. Ten to 30 minutes after the onset of clinical reaction, the first postreaction sample contained a tryptase level of 13.8 ng/ml. A peak level of 51.9 ng/ml was measured 135 minutes after onset of the reaction, by which time FEV_1 values had returned to normal, perhaps as a result of treatment with metaproterenol. A tryptase level 5½ hours after onset of the reaction was still elevated (24.4 ng/ml) during a time when nasoocular symptoms persisted but 3 hours after gastrointestinal symptoms had ended. In Fig. 2 are depicted data from S. G.'s reaction. The tryptase levels measured at 20, 40, and 70 minutes postreaction were increased, 20.6 to 29.8, peaking at 40.0 ng/ml. In this case, the peak tryptase level preceded the lowest FEV_1 value by 40 minutes. Five hours after the onset of this reaction, the serum tryptase level continued to be elevated (16.8 ng/ml) at a time when FEV_1 values had returned to normal, systemic flush and diarrhea had subsided, but nasal congestion had persisted. Based on these elevated levels of tryptase in the serum, all or part of the reactions was consistent with release of MC mediators and their effects on target organs.

As presented in Table IV, at the end of ASA desensitization, when each of the 17 subjects ingested 650 mg of ASA without adverse clinical effect, serum tryptase levels, obtained 3 hours after ASA, 650 mg, were <2.5 ng/ml.

Plasma histamine levels

Plasma histamine levels from baseline and as soon as possible after onset of reaction are listed in Table IV. Plasma from subjects R. M. and S. G. demonstrated a significant increase in histamine values at the time of clinical reaction compared with baseline levels (Δ histamine value: R. M., 414 pg/ml; Δ histamine values: S. G., 179 pg/ml). Plasma from G. R. demonstrated a definite but smaller increase (Δ histamine value: G. R., 119 pg/ml) at time of onset of ASA-induced reaction. The mean Δ plasma histamine value for these three subjects (238 pg/ml) was significantly greater than the mean Δ for the other 14 subjects (9 pg/ml), $p < 0.04$. A few of the other subjects were found to have small increases in histamine (D. K. with mild flushing, demonstrated an increase from 43 to 139 pg/ml, and K. W., P. M., and P. P. demonstrated a rise of >30 pg/ml), but most values at re-

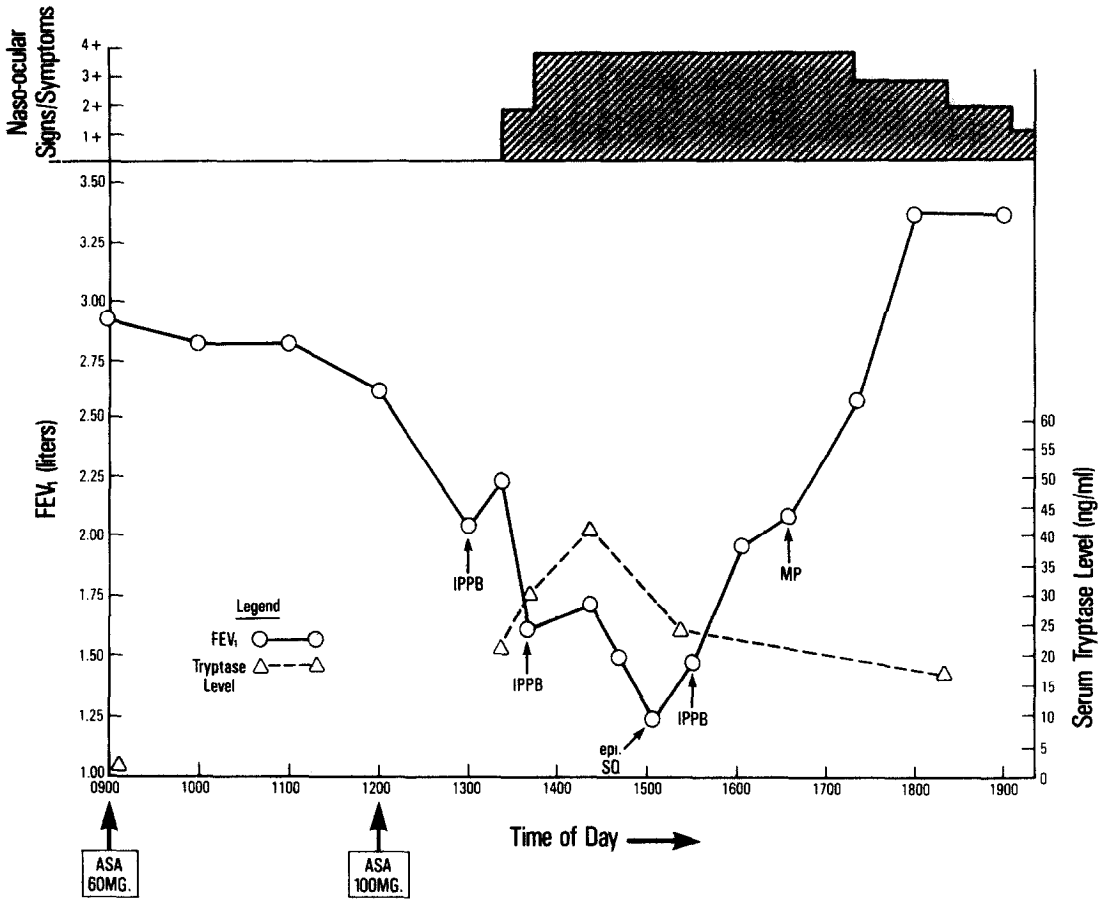

FIG. 2. In subject S. G., ASA-reaction onset occurred at 1300 hours. Tryptase release, peaking at 40.0 ng/ml, was measured during profound bronchospasm (FEV_1, 58% below baseline) and nasoocular reaction (4+) in addition to a cutaneous (severe flushing) and gastrointestinal (diarrhea) response lasting from 1330 to 1500 hours.

action were the same or below baseline values. As a group of 14 patients, statistical analysis of the mean histamine levels, comparing before reaction with reaction with Student's paired t tests, were $p > 0.05$, or not significant. After ASA desensitization, individual plasma histamine levels were lower than baseline values in 9/17 subjects, including patient S. G. In 8/17 subjects, histamine levels were elevated in the acute desensitization samples. The mean post-ASA desensitization histamine level for the group was 110 pg/ml, as contrasted to the baseline mean of 76 pg/ml. This difference was not statistically significant with a $p > 0.05$.

Other statistical studies

Regression analysis contrasting either tryptase or histamine levels with changes in FEV_1 values were not significant.

DISCUSSION

Evidence for MC activation during ASA-induced respiratory reactions was found in three of 17 sensitive subjects on the basis of elevations of serum tryptase and plasma histamine levels. None of the remaining 14 ASRA subjects, with ASA reactions limited to a respiratory response, had detectable tryptase in their serum; patient D. K., however, with mild flushing in addition to his respiratory reaction, experienced a modest rise in histamine at the onset of clinical reaction.

The specificity of tryptase as a marker for human MCs has been demonstrated in previous studies by immunohistochemical and biochemical techniques.[8-11, 16, 17] Tryptase is a preformed mediator, stored along with histamine and proteoglycan in the secretory granules of MCs. The degranulation of MCs, whether by immunologic or nonimmunologic mechanisms and regardless of the inhibition of prostaglandin synthesis, is accompanied by the release of this enzyme. The systemic reactions experienced by three subjects in the current study and by two subjects reported previously[12, 14] were associated with elevated levels of serum tryptase. MC activation therefore is implicated in some ASA-induced reactions and ap-

pears to correlate with reactions extending beyond the respiratory tract.

For those subjects with reactions limited to the respiratory tract, serum tryptase levels were not detectably elevated, and rises in histamine levels were modest, if they occurred at all. Differences in the magnitude of the respiratory reactions cannot explain these findings, since patient R. M., with the highest peak tryptase level (51.9 ng/ml), experienced bronchospasm with an FEV_1 value declining by 31%. Five of the 14 patients without elevated tryptase levels in their sera experienced bronchospasm, with FEV_1 values between 31% and 58%. Whether this reflects a limited ability of mediators released in respiratory tissue to enter the circulation, an insufficient magnitude or speed of release of mediators to raise systemic levels, or lack of involvement of MCs in these latter patients' reactions is not known. In those subjects with modest elevations in histamine but not tryptase, basophils could be the source of the histamine. Interestingly, the two patients with the largest rise in tryptase reacted to a 100 mg dose of ASA, whereas provoking doses of ASA for all other subjects, except N. C., were 60 mg or less. Dose-dependent reactions occur after ASA challenge, suggesting the possibility that challenge of these two subjects with larger doses of ASA might have induced a larger, perhaps systemic, response, with associated elevated levels of histamine and tryptase anticipated. More than one cell type may be activated in ASA-induced reactions, each cell type requiring a different threshold concentration of ASA to induce a response.[7, 18, 19] However, against MC activation requiring a higher ASA-provoking dose, patient N. C. received 150 mg of ASA with only a 23% decline in FEV_1 and no elevation of either tryptase or histamine. We are more inclined to anticipate that the state of activity of pulmonary cells, including macrophages, MCs, and EOSs, is likely to be important in the dosage of ASA required to induce the reaction and the degree of severity of the reaction itself.

After ASA-induced reaction, the release of tryptase into the circulation appears to occur more gradually than histamine release. In the current study, three patients with ASA-induced symptoms extending beyond the respiratory tract demonstrated significant histamine release at the onset of the clinical reaction. This finding was similar to that in a previous study in which histamine was elevated shortly after the onset of ASA-induced respiratory reactions, particularly when flushing and gastrointestinal symptoms also occurred.[19] These three subjects exhibited peak levels of tryptase at 1 to 2 hours after the onset of clinical reactions. The time course during anaphylaxis to a bee-sting challenge has been studied in detail; peak levels of tryptase were observed 1 to 2 hours after the sting and then declined under apparent first-order kinetics with a half-life of $\approx$2 hours, whereas peak levels of histamine occurred 5 minutes after the sting and returned to baseline by 15 to 30 minutes. Both disassociation of histamine and tryptase from granule matrix within the MC and extrusion of these products through cell membranes govern the kinetics of histamine and tryptase release into extracellular spaces.

In the current study, neither the provoking dose of ASA nor the time to onset of clinical symptoms can be predicted accurately, and onset of reaction was difficult to establish precisely. Therefore, blood sampling began after the observed onset of clinical reactions (FEV_1 declined by 20% or more). In most patients, nasoocular symptoms and signs preceded a decline in FEV_1 values but are difficult to identify in their earliest phase. Histamine levels may have risen and returned to baseline before sampling. In addition, Simon et al.[20] have demonstrated that spontaneous histamine release, with elevated plasma levels, occurs frequently during increased asthma activity of any type, even when release was not associated with ASA-induced reactions. However, in evaluating ASA-induced respiratory reactions, measurement of tryptase appears to be a more practical and specific marker of MC activation than is histamine.

Activation of MCs may account for some or all of the features of ASA-induced reactions. Histamine, LTC_4, and prostaglandin D_2 are released or formed by MCs and have potent effects on the vasculature and smooth muscle in lung, skin, and gastrointestinal tissues.[7] Histamine is capable of inducing the gastrointestinal and cutaneous reactions and may be the major mediator in systemic symptoms extending beyond the respiratory tract. Indirect support for this idea is the study by Szczclik and Senwenska[21] who pretreated ASA-sensitive patients with an antihistamine and were able to either block or ameliorate the systemic or nasoocular symptoms, but not the bronchospastic response, in patients challenged with ASA. Similar blocking studies with cromolyn have prevented or delayed asthmatic responses to ASA challenges,[22] suggesting that MC products, such as leukotrienes, may induce the bronchospastic response to ASA. In urine samples, elevated levels of LTE_4, a metabolite of LTC_4,[23] and of LTC_4 in nasal lavage fluid[7] were found in sensitive subjects with asthma after ASA challenge, but not in control subjects undergoing similar exposure to ASA. Leukotrienes, formed from lipid membranes of MCs, macrophages, and EOS, are good candidates to induce severe and prolonged bronchospasm, a characteristic clinical pattern in ASA-induced respiratory reactions.[7] In addition, amplification of the local tissue response to MC activation may occur by recruitment and activation of other cells, for

example, secretion of LTB_4 may attract neutrophils, and secretion of platelet-activating factor may attract EOSs. It appears likely that a concert of cells and mediators are responsible for the ASA-induced reactions. Leukotrienes may produce prolonged bronchospasm and histamine may produce immediate bronchospasm, as well as other extrapulmonary effects. Other mediators await further definition and clarification of their roles.

Tryptase levels in the serum of ASA-desensitized subjects were not elevated. Histamine levels were inconsistent after acute ASA desensitization, tending to be slightly lower in most patients, a finding consistent with previous studies of desensitized subjects.[7] In those subjects with higher postdesensitization histamine levels, it is possible that ASA desensitization was not completed at the cellular level, even though clinical reactions were not observed. Additional sampling after long-term ASA desensitization will be necessary to answer this question. Thus, ASA desensitization appears to attenuate the MC response to ASA.

In summary, MC activation occurs during the systemic response to ASA challenge in some sensitive subjects. Whether this reflects a direct or indirect effect of ASA on MCs and to what extent other cell types are involved was not addressed in these studies. Additional studies are also needed to measure localized release of tryptase in the respiratory tract, perhaps in ocular, nasal, or bronchial fluids, to assess whether or not local MC activation occurs in most ASA-sensitive subjects with asthma who do not generate serum levels of tryptase during ASA-induced respiratory reactions.

We are indebted to the nursing and laboratory staff of the GCRC for their invaluable assistance in performing the protocol. We thank the word processing staff of the Department of Molecular and Experimental Medicine for their assistance in preparation of this manuscript, and Diana Dull for technical assistance with tryptase measurements.

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