Cardiac Anaphylaxis
Complement Activation As an Amplification System

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Complement is activated, and C3a and C5a anaphylatoxins are generated during hypersensitivity reactions clinically associated with cardiopulmonary collapse. The administration of C3a or C5a to nonsensitized isolated guinea pig hearts mimics the events caused by antigen challenge of sensitized hearts (i.e., cardiac anaphylaxis) in the absence of complement. Thus, complement-derived anaphylatoxins may participate in immediate hypersensitivity reactions in which the heart is a target organ. To assess the contribution of complement activation and anaphylatoxin generation to cardiac dysfunction, we have elicited anaphylaxis in isolated guinea pig hearts in the presence of complement and found that the ensuing dysfunction is markedly enhanced. This amplification is most likely attributable to anaphylatoxin formation because 1) inactivation of C3 or selective C3 depletion, i.e., the loss of the component responsible for the formation of the anaphylatoxins C3a and C5a, prevents complement-induced exacerbation of cardiac anaphylaxis, whereas reconstitution with C3 and C5, or even only C3, restores it; in fact, the greater the C3 content at the time of antigen challenge, the more intense the anaphylactic crisis; and 2) the severity of cardiac anaphylaxis is markedly reduced by preexposure to C3a, and this reduction is directly related to the dose of C3a injected and to the amount of endogenous cardiac histamine depleted by C3a before antigen challenge. Complement-derived anaphylatoxins appear to promote the same mediator release that has been initiated by the antigen-antibody reaction; thus, complement activation functions as an amplification system in cardiac anaphylaxis.

(Circulation Research 1989;65:847-857)

Complement activation and generation of C3a and C5a anaphylatoxins, fragments of the third and fifth complement components, respectively, likely occur during hypersensitivity reactions.1,2 Particularly high plasma levels of C3a and/or C5a have been associated with cardiopulmonary collapse during hypersensitivity reactions in humans.3,4 The administration of purified human C3a or recombinant human C5a anaphylatoxins into isolated nonsensitized guinea pig hearts causes a dysfunction that is qualitatively similar to that elicited by antigen challenge of sensitized hearts.5-7 The finding that anaphylatoxins mimic cardiac anaphylaxis prompted us to determine whether complement is activated and anaphylatoxins are generated in the course of immediate hypersensitivity reactions of the heart. We found that complement activation and anaphylatoxin generation do occur when anaphylaxis is elicited in isolated atrial and ventricular myocardial preparations in the presence of a source of complement.7 We also found that complement activation is associated with chronotropic and inotropic changes and that these responses are enhanced if anaphylatoxin inactivation is prevented.7 Accordingly, anaphylatoxins generated as a result of complement activation during immediate hypersensitivity reactions may contribute to anaphylactic cardiac dysfunction. To verify this hypothesis and to quantify the plausible contribution of complement activation, we have compared cardiac anaphylaxis elicited in the presence of serum as a source of complement with the reaction obtained in its absence.

We report that cardiac anaphylaxis is exacerbated in the presence of serum, that this amplification is lost when C3-deficient serum is used, and that C3 reconstitution recovers the severity of the reaction. We also report that pretreatment of sensitized guinea pig hearts with C3a anaphylatoxin alleviates the dysfunction elicited by subsequent antigen challenge. Because anaphylatoxins and the reaction between antigen and mast cell-bound antibodies...
ultimately involve the release of common mediators, activation of complement with the concomitant liberation of anaphylatoxins may serve as an important amplification system of cardiac anaphylaxis.

Materials and Methods
Isolated Heart Anaphylaxis

Male Hartley guinea pigs (250-300 g) were passively sensitized by injection of 0.1 ml guinea pig antiserum that contained 4 mg/ml each of antidinitrophenyl-bovine γ-globulin IgG, and IgG₂. Of the two immunoglobulin subclasses, only IgG₁ is cytotoxic in the guinea pig. Twelve to 14 hours later, the animals were lightly anesthetized with CO₂ vapors and killed by cervical dislocation. The hearts were excised and perfused in a Langendorff apparatus at a constant pressure of 40 cm H₂O. Each perfusing solution was oxygenated with 95% O₂-5% CO₂ and warmed to 33° C. This temperature was selected to minimize spontaneous complement activation. Isometric ventricular contractions and bipolar surface electrograms were continuously recorded from the right atrium and left ventricle. Coronary flow rate was continuously monitored by measuring the volume of coronary effluent collected during 2-minute periods. Sinoatrial rate, contraction, coronary flow rate, and electrogram remained constant for at least 3 hours in control conditions, an indication that the hearts were adequately oxygenated.

The hearts were first perfused with Ringer’s solution for 30-45 minutes until sinoatrial rate, contraction, coronary flow rate, and electrogram remained constant for at least 3 hours in control conditions, an indication that the hearts were adequately oxygenated.

The hearts were then challenged intra-aortically with 1 mg dinitrophenyl-bovine serum albumin in 0.4 ml warm oxy-
Anaphylatoxins Amplify Cardiac Anaphylaxis

Figure 2. Graphs showing inactivation of selected complement components and effect on cardiac anaphylaxis. Hearts were perfused with the following: column A, serum in Ringer's (1:10 dilution; control); column B, serum in which complement components C3, C4, and C5 were chemically inactivated; column C, chemically inactivated serum reconstituted with C3 alone; and column D, chemically inactivated serum reconstituted with both C3 and C5. Bars are mean±SEM (A, n=8; B, n=6; C, n=6; D, n=6) of (from top to bottom) onset and duration of atrioventricular (AV) conduction block, decrease in coronary flow rate (maximum change within 20 minutes after antigen challenge), histamine release (total amount released in 20 minutes after antigen challenge minus basal release), and C3 consumption (maximum consumption in 20 minutes after antigen challenge). *Significantly different from control (p<0.05) as determined by analysis of variance followed by Dunnett's t test. Control values in 10% serum (n=8) were as follows: sinoatrial rate, 218±6 beats/min; P-R interval, 65.6±3.2 msec; left ventricular contractile force, 7.2±0.5 g; coronary flow, 5.5±0.35 ml/min; histamine release, 186±50 ng/ml/min. Control values in dialyzed serum (n=18) were (in the same order) 206±8 beats/min, 60.7±2.8 msec, 6.6±0.3 g, 4.8±0.8 ml/min, and 177±47 ng/ml/min. The two control groups were not significantly different.

Solutions for Perfusion of the Isolated Heart

Ringer's solution. The composition of the Ringer's solution was as follows (mM): Na+ 160, K+ 5.6, Ca2+ 2.2, Cl− 164, HCO3− 5.9, and glucose 5.5.

Normal GPS. Normal GPS (Colorado Serum, Denver, Colorado) was diluted 1:10 (vol:vol) with Ringer's solution.

Chemical depletion of selected complement components in GPS. Normal GPS was incubated with an equal volume of cold 1 M potassium thiocyanate for 24 hrs at 4° C (i.e., conditions known to inactivate the third, fourth, and fifth complement components C3, C4, and C5 in human serum).12 The mixture was then treated for 45 minutes at 37° C with a final concentration of 0.015 M hydrazine hydrate, an additional procedure required for full inactivation of C3, C4, and C5 in GPS.13 After
extensive dialysis at 4°C against saline (four changes in 48 hours), the treated serum was stored at 4°C until use (within 24 hours). Inactivation of C3, C4, and C5 was confirmed by hemolytic assay and was found to be greater than 97%. For use, this reagent was diluted 1:10 (vol:vol) with Ringer's solution, and the ion concentration in the saline-serum solution was adjusted to obtain the same concentration of the Ringer's solution. As saline contains 0.85% sodium chloride, all ions and glucose were added to the solution depending on the volume of the reagent after dialysis.

Reconstitution of chemically depleted GPS with C3 and C5. Purified human C3 and C5 were added to GPS chemically depleted of C3, C4, and C5 to a final concentration of 0.34 mg/ml and 50 μg/ml, respectively, before diluting the reagent 1:10 with Ringer's solution. Reconstitution of C3 hemolytic activity was shown to be 21%.

Immunodepletion of C3 in GPS. Normal GPS was selectively depleted of C3 by affinity chromatography as follows: the IgG fraction of goat anti-guinea pig C3 was coupled to activated Sepharose 4B (Pharmacia LKB, Piscataway, New Jersey). Thirty milliliters normal GPS were added to 20 ml anti-guinea pig C3-Sepharose in a tube that wasrotated at 4°C for 45 minutes. The mixture was centrifuged, and the reagent was collected and the on-set of C3a administration, the same heart was challenged with specific antigen as described above. As control, guinea pigs were injected with 0.1 ml guinea pig serum 12–14 hours before the beginning of the experiment.

Histamine Dose-Response in Isolated Hearts Previously Treated With C3a

Histamine was injected intra-aortically in increasing doses of 0.1, 0.3, 1.0, 3.0, 10, and 30 μg into isolated nonsensitized guinea pig hearts, either untreated or previously treated with C3a (1 μg). This dose of C3a causes a 5–10% change in cardiac function (i.e., an increase in sinoatrial rate, a prolongation of P-R interval, a decrease in left ventricular contractile force, and a decrease in coronary flow rate) compared with baseline parameters preceding C3a administration. Ten to 15 minutes after C3a administration, cardiac function returned to pre-C3a baseline levels, and a histamine dose-response relation was obtained in each heart.

Statistical Analysis

Differences between mean responses comparing two groups were determined by two-tailed Student's t test with a level of significance of p < 0.05.
Differences between mean responses comparing more than two groups were determined by analysis of variance followed by two-tailed Dunnett's t test with $p<0.05$ as the limit of significance. 18

Results

Cardiac Anaphylaxis in the Presence and Absence of a Source of Complement: A Quantitative Comparison

As shown in Figure 1, the reaction of sensitized guinea pig hearts to challenge with specific antigen was characterized by tachycardia, slowing of atrioventricular conduction (i.e., increase in P-R interval) culminating in conduction block, a brief increase followed by a prolonged decrease in left ventricular contractile force, decrease in coronary flow rate, and histamine release. The anaphylactic dysfunction in hearts perfused with Ringer's solution alone was compared with the anaphylactic dysfunction in hearts perfused with Ringer's solution in the presence of serum as a source of complement (i.e., 10% serum in Ringer's) (Figure 1). In the presence of complement, conduction arrhythmias started earlier (33.6±1.8 vs. 57.6±5.4 seconds; $p<0.02$) and lasted longer (7.9±1.3 vs. 4.1±0.85 minutes; $p<0.05$). In addition, the initial transient positive inotropic effect (expressed as maximal change occurring within 30 seconds from antigen challenge) was greater (27.3±5.6% vs. 15.6±5.8%, $p<0.05$), and the decrease in coronary flow rate was also greater ($-44.3±2.8%$ mean change over 10 minutes vs. $-9.7±1.5%$; $p<0.02$). Sinoatrial rate (expressed as maximal increase occurring within 5 minutes from antigen challenge) was significantly greater in serum-perfused hearts than in Ringer's-perfused hearts (66±4 vs. 50±3 beats/min (see Figure 1A). These changes were accompanied by a larger histamine release into the coronary effluent, which totaled 2.9±0.22 µg/g in serum-perfused hearts as opposed to 1.29±0.28 µg/g in hearts perfused with Ringer's solution ($p<0.001$) during 20 minutes after antigen challenge. In hearts perfused with 10% serum solution, all of these changes were accompanied by consumption of C3, an indication of complement activation (see Figure 1F). The time courses of C3 consumption and histamine release in serum-perfused hearts were very similar; both histamine release and C3 consumption reached a peak within 2 minutes after antigen challenge and declined thereafter, returning within 10 minutes to levels preceding antigen challenge. Antigen challenge of serum-perfused nonsensitized hearts failed to elicit any change in cardiac function, and C3 consumption was insignificant (1.05±1.05%; mean±SEM; $n=4$).

The Role of C3 in Cardiac Anaphylaxis: Selective Depletion and Reconstitution

To determine whether complement activation may be responsible for the amplification of the anaphylactic reaction, we induced anaphylaxis in hearts perfused with 10% serum in which C3, C4, and C5 had been chemically inactivated. As shown in Figure 1, the anaphylactic reaction in hearts perfused with complement-inactivated serum was greatly attenuated as compared with the reaction in hearts perfused with untreated serum. Thus, in the absence of functionally active complement components C3, C4, and C5, arrhythmia was delayed in onset and was shorter in duration, coronary flow rate was

![Figure 3](http://circres.ahajournals.org/)
much less decreased, and histamine release was markedly reduced. In contrast, chronotropic and inotropic responses were not significantly different in the absence or presence of C3, C4, and C5; the chronotropic response was already maximal in the absence of C3, C4, and C5 and, thus, could not increase any further in the presence of these complement components, and the inotropic response was obscured by the concomitant arrhythmic events, independently of the presence or absence of C3, C4, and C5.

An alternative method in which C3 was selectively immunodepleted by affinity chromatography confirmed that complement inactivation was responsible for the attenuation of anaphylactic dysfunction in serum-perfused hearts. In the two hearts perfused with C3-immunodepleted serum, anaphylactic histamine release was approximately halved, the time to onset of arrhythmia was nearly doubled, the duration of arrhythmia was shortened by more than 60%, and the decrease in coronary flow rate was alleviated by approximately 40% (Table 1). Thus, the alleviation of cardiac anaphylactic dysfunction by C3 immunodepletion was similar to that obtained with chemical inactivation of C3, C4, and C5.

We next verified whether reconstitution of the missing complement components would restore the severity of anaphylactic dysfunction to its predemotion level. We found that the addition of 0.34 mg/ml purified human C3 (i.e., approximately equal to one third of the normal serum concentration) to the chemically inactivated serum restored 40-70% of the cardiac anaphylactic response as determined by onset and duration of arrhythmias, decreased coronary flow, and histamine release (Figure 2). Furthermore, when 1 mg/ml C3 (i.e., equal to the normal serum C3 concentration) was added to the immunodepleted serum, 65-100% of the cardiac anaphylactic dysfunction was reinstated (Table 1). Therefore, reconstitution of C3 activity in serum in which C3, C4, and C5 were chemically inactivated or in which only C3 had been selectively immunodepleted (Figure 2 and Table 1) restored the severity of cardiac anaphylaxis to that observed with normal serum.

As shown in Figure 3, the duration of arrhythmias, the magnitude of the decrease in coronary flow, and the amount of histamine released during anaphylaxis all directly correlated with the quantity of C3 available at the time of antigen challenge. Thus, independently of whether the perfusing serum...
Modification of Cardiac Anaphylaxis by Pretreatment With C3a Anaphylatoxin

As shown in Figure 4, the cardiac effects of C3a anaphylatoxin resemble, from a qualitative standpoint, those observed in sensitized guinea pig hearts upon challenge with specific antigen; however, the anaphylactic reaction was much less severe in hearts preexposed to C3a at the dose indicated on the abscissa (Figure 4). This suggests that C3 played a major role in determining the severity of the anaphylactic crisis.

Modification of Cardiac Anaphylaxis by Pretreatment With C3a Anaphylatoxin

As shown in Figure 4, the cardiac effects of C3a anaphylatoxin resemble, from a qualitative standpoint, those observed in sensitized guinea pig hearts upon challenge with specific antigen; however, the anaphylactic reaction was much less severe in hearts preexposed to C3a (10 μg) than in control hearts. In fact, as shown in Figure 5, with increasing C3a doses, the anaphylactic impairment in atrioventricular conduction was progressively less severe (i.e., the P-R interval was less prolonged and atrioventricular conduction block was shorter), and the increase in sinus rate and the decrease in coronary flow were of lesser magnitude. The reduction in anaphylactic dysfunction by prior exposure to C3a was associated with definite changes in mediator release. As shown in Figure 6, progressively greater amounts of endogenous cardiac histamine were released with increasing doses of C3a, whereas progressively less histamine was released by subsequent antigen challenge. Thus, the severity of cardiac anaphylaxis was inversely related to the dose of C3α to which the heart had been preexposed and was also inversely related to the amounts of endogenous histamine released in response to C3a. This suggested that anaphylactic cardiac dysfunction was mitigated by prior exposure to C3a because C3a had already caused the release of histamine and possibly of other anaphylactic mediators.

Yet, the possibility that C3a-pretreated hearts were less responsive to antigen challenge not because they had already released the anaphylactic mediator...
Figure 7. Graphs showing cardiac effects of histamine and their modification by pretreatment with complement component fragment C3a. Dose-response relations are shown for the effects of histamine (administered by intra-aortic bolus injection) on sinoatrial rate (lower panel), duration of P-R interval (upper panel), and incidence of atrioventricular (AV) conduction block (inset) in control hearts (i.e., injected intra-aortically with saline 20 minutes before the first dose of histamine) and in hearts pretreated with C3a (1 μg; intra-aortic injection 20 minutes before histamine). Points (mean±SEM; n=6, control; n=6, C3a-pretreated) represent maximum changes from values immediately preceding each histamine injection; these changes are expressed as percent of the maximum response, which, in the controls, occurred with the 30 μg histamine dose. *ED50 values (horizontal bars, 95% confidence limits). Control values before histamine administration were 240±6 beats/min for sinoatrial rate and 57.5±2.6 msec for P-R interval. Control values before histamine, but after C3a, were 243±6 beats/min and 56±2.2 msec, respectively.

but because they had become less sensitive to the effects of the mediator also had to be considered. As shown in Figure 7, however, the response to histamine (0.1–30 μg) of nonsensitized guinea pig hearts pretreated with C3a (1 μg) was greater than that of control hearts. Thus, the concentration-response relations for the positive chronotropic and negative dromotropic effects of histamine were shifted upwards and to the left after exposure to C3a; moreover, the incidence of histamine-induced atrioventricular conduction block increased in hearts pretreated with C3a.

Discussion

The postulate of this study was that complement-derived anaphylatoxins are putative mediator-modulators of immediate hypersensitivity reactions in which the heart is a target organ.7 The purpose of our investigation was to verify this hypothesis by quantitatively assessing complement activation and its relative contribution to anaphylactic cardiac dysfunction. Our results clearly demonstrate that cardiac anaphylaxis is markedly enhanced in the presence of a source of complement. Two major lines of evidence support the concept that this amplification is attributable to anaphylatoxin formation. First, inactivation of C3 or selective C3 depletion (i.e., the loss of the component responsible for the formation of the anaphylatoxins C3a and C5a) prevents complement-induced exacerbation of cardiac anaphylaxis; reconstitution with C3 and C5, or even only C3, restores it. Indeed, the greater the C3 content at the time of antigen challenge, the more intense the anaphylactic crisis. Second, the severity of cardiac anaphylaxis is markedly reduced by preexposure to C3a, and this reduction is directly related to the dose of C3a injected and to the amount of endogenous cardiac histamine released by C3a. Complement-derived anaphylatoxins appear to promote the same mediator release that has been initiated by the antigen-antibody reaction; thus, complement activation functions as an amplification system in cardiac anaphylaxis.

It is well established that activation of C3 is essential for the production of both C3a and C5a anaphylatoxins; since C3 consumption is a measure of C3 activation, consumption of C3 is strongly suggestive of anaphylatoxin production.19 Because of the unavailability of a radioimmunoassay specific for guinea pig C3a and/or C5a, we could not assay directly for anaphylatoxin; nevertheless, it is reasonable to assume that C3a was produced during cardiac anaphylaxis. Indeed, we have recently demonstrated that anaphylatoxin production is directly correlated with C3 consumption during immediate hypersensitivity reactions in isolated guinea pig atria and papillary muscle bathed in diluted human serum as a source of complement.7 We have also obtained evidence that the anaphylactic positive chronotropic and inotropic responses of isolated atria and papillary muscle are positively correlated with the amounts of endogenous histamine released by anaphylatoxin and are magnified when inactivation by serum carboxypeptidase N is inhibited.7 In fact, in addition to atrioventricular conduction block,
which invariably occurred in serum-perfused ana-
phylactic hearts (see Figure 1), we have noted severe idioventricular tachyarrhythmias in four and ventricular fibrillation in two of six hearts in which anaphylatoxin inactivation was prevented by a serum carboxypeptidase N inhibitor (U. del Balzo, unpublished observations).

Hence, C3 activation in cardiac anaphylaxis may serve as an amplifying mechanism, and this amplification may be mediated by the C3-dependent formation of the anaphylatoxins. Indeed, we had previously shown that the injection of C3a and C5a into isolated guinea pig hearts causes an anaphylactic-like dysfunction due to the release of various hypersensitivity mediators, including histamine. Therefore, we assumed that C3a magnifies cardiac anaphylaxis by promoting the release of the very mediators that are released by antigen bridging of two antibody molecules on the mast cell membrane. If so, pretreatment of guinea pig hearts with C3a should attenuate the dysfunction elicited by subsequent exposure to the sensitizing antigen.

We found this to be the case. In fact, the intensity of the anaphylactic crisis was reduced by preexposure to C3a, and the severity of the reaction was progressively abated with increasing doses of C3a that released increasing amounts of endogenous cardiac histamine (see Figures 4–6). A protection from anaphylaxis by pretreatment with anaphylatoxin had been previously noted in vivo. 20,21

It is unlikely that the reduction in the severity of cardiac anaphylaxis by pretreatment with C3a is due to end-organ histamine desensitization. Although C3a, either exogenously administered or endogenously generated, liberates histamine from cardiac stores, the cardiac effects of histamine are not subject to tachyphylaxis. Furthermore, we found that preexposure to C3a potentiates the cardiac effects of histamine, as evidenced by a greater tachycardia, a larger increase in P-R interval, and a greater incidence of arrhythmias in hearts pretreated with C3a (see Figure 7).

Collectively, our cross-tachyphylaxis experiments and those from other laboratories indicate that anaphylatoxin and anaphylaxis are likely to share common mechanisms of action and that the complement-induced amplification of immediate hypersensitivity reactions of the heart, as monitored by C3 consumption, is mediated by complement-derived anaphylatoxins. This view is consistent with evidence implicating the anaphylatoxins as important mediators of hypersensitivity reactions and as potent biological peptides capable of profound effects on a variety of organs, including the heart. Moreover, anaphylatoxins induce the release of mediators of hypersensitivity from many tissues, including the heart.

Several recent studies support the role of anaphylatoxins as mediators of the pathophysiological changes associated with hypersensitivity reactions. These studies demonstrate complement component and C3a and/or C5a generation in blood of patients undergoing anaphylaxis provoked by a variety of agents. The latter include insect stings, drugs, house dust, intravenous injections of radiocontrast media, dialysis membranes, and inhalation challenge in asthmatic patients. Most important, the circulating levels of anaphylatoxins appear to directly correlate with the severity of clinical symptoms. These reactions range from severe urticaria and angioedema to life-threatening bronchospasm, diffuse coronary artery spasm, angina, tachycardia, decreased cardiac output, hypotension, and cardiopulmonary collapse. Thus, our findings characterize a clinically relevant in vitro model of antigen-triggered, anaphylatoxin-amplified, immediate hypersensitivity reactions of the heart.

The mechanism of complement activation during immediate hypersensitivity reactions remains unclear. Only certain immunoglobulin types (e.g., human IgE and guinea pig IgG,) fix to mast cells and basophils, both of which secrete anaphylactic mediators. Guinea pig IgG and human IgE antibodies, in the form of immune precipitates, activate complement via the alternative pathway. Because the presence of C4 is necessary for complement activation via the classical pathway, our finding that complement is still activated during IgG-mediated cardiac anaphylaxis in the absence of C4 (i.e., in hearts perfused with C3-, C4-, and C5-depleted serum reconstituted with C3 and C5 only) implies that in this model, complement activation may occur via the alternative pathway. However, complement activation could occur independently of either the classical or the alternative pathway. Activation may occur indirectly via the induction of proteolytic enzymes that can cleave several complement components simultaneously, including C3, C5, and C-derived chemotactic peptides, probably released by tissue proteases, have been detected in nonimmunological inflammation such as myocardial infarction, consumption of classical complement components has also been demonstrated in the heart of patients with myocardial infarction. C3-cleaving enzymes are probably released from damaged cells since they can be extracted from normal tissue. Mast cells and basophils contain a number of neutral proteases in their secretory granules. Release of these enzymes occurs in parallel with histamine release upon stimulation of the cells with IgE and antigen. Direct enzymatic digestion by celluloarly derived proteases can lead to the depletion of complement. Trypsin-like, the dominant neutral protease of human pulmonary mast cell secretory granules, has the capacity to generate C3a anaphylatoxin from purified human C3 in vitro. Thus, a variety of proteolytic enzymes could potentially participate in complement activation independently of the well-established classical and alternative pathways. Thus, mast cell–coupled activation and secretion of a C3-cleaving enzyme leading to generation of C3a anaphylatoxin may represent a
mechanism of modulation-amplification of immediate hypersensitivity reactions.

In conclusion, our findings indicate that the complement system functions as an important amplifier in immediate hypersensitivity reactions in which the heart is a target organ. It appears that anaphylatoxin generation is the primary mechanism of this amplification. Because cardiac dysfunction ultimately results from the actions and interactions of many mediators of inflammation and hypersensitivity, we propose that the role of anaphylatoxins in cardiac anaphylaxis is to further the mediator release that has been triggered by the antigen-antibody reaction.

Acknowledgments

We wish to express our gratitude to Dr. Aida A. Chenouda for technical help and to Mrs. Irene Stellaccio-Franklin for secretarial assistance.

References


KEY WORDS: complement activation • anaphylatoxins • C3a • C5a • anaphylaxis, complement and cardiac • C3 depletion • C3 reconstitution
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doi: 10.1161/01.RES.65.3.847

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

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