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A MOLECULAR BASIS FOR THE IMMEDIATE HYPER-SENSITIVITY, (U)
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HYPER-SENSITIVITY

by

E. Bekier and W. Kazimierczak

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A MOLECULAR BASIS FOR THE IMMEDIATE HYPER-SENSITIVITY

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At present about 25-30% of the total human population suffers from allergies and a constant upward trend has been observed in the last few years. One of the factors responsible for this increased occurrence of allergic diseases is the constant industrial development of the modern world.

The necessary conditions to produce an allergic state is for the allergen to enter the body. Allergens can enter the body via various routes: respiratory tract, skin, digestive system. Each of those systems is protected by natural defense mechanisms. For the respiratory tract they are: mucous, cilia or the very thin layer of an active layer surface of the alveoli. There are corresponding defense mechanisms for the skin and digestive tract. Those natural defenses are very effectively destroyed by the industrial dusts, detergents, food preservatives, etc. When the "gates" become open, and they are open more and more so in the modern world, various substances can penetrate into the body and act as a potential antigens.

The widespread presence of the allergens in the environment does not necessarily produce hypersensitivity in all individuals, but only in those in the so-called state of atopy. The notion of atopy was introduced by Coca and Cooke to describe hereditary or acquired hypersensitivity of the individual to the development of the allergic reaction.

Role of the antibodies in the allergic reaction

Allergies manifest themselves with a great variety of symptoms, such as asthma, skin eruptions, migraine, hay fever, changes in blood vessels, and some kidney and digestive tract diseases. What all of them have in common is the pathogenic mechanism. The essence of the allergic diseases is the release by the tissues substances having great biological activity: mediators of the

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allergic reactions which act upon the effectors. The binding of the antigen with the antibodies located on the surface of the effector cells initiates the release of the mediator.

Cells which react when antigens enter the body and which initiate the immunological response being the antibody production, are small lymphocytes or so-called competent immunological cells. Already in the fetus precursors of the lymphocytes divide into cells of the type T (thymus) and B (Bursa Fabricii). T-cells do not produce classical antibodies, but serve as mediators for the cell resistance (Miller and Mitchel, 1967). They produce the factor inhibiting the migration of leukocytes (MIF) and other substances which do not exhibit immunological specificity. (Bloom and Bennet, 1970). T-cells act as so-called "killer cells", in transplants and cancer response. (Miller et al., 1971). B-cells are the ones responsible for the production of immunoglobulin having antibody activity which participates in the immediate reaction. The latter cells are mostly located in the porous linings of the respiratory and digestive tracts and in the regional porous joints (Tada and Ischizaka, 1970).

The nature and quantity of the synthesized antibodies depend on the individual on the amount of the antigen, and on the way it was introduced into the system.

Allergy can be passively transferred via the serum of the allergic individual. It was demonstrated in 1921, at the medical society meeting, when doctors Carl Prausnitz and Heinz K~~i~~stner (one of them was suffering from hay fever and another was allergic to fish), administered to each other under skin injections of their own serum. This is a classic test, today called the P-K test. About 46 years later, in 1967, Japanese researchers (Ishizaka and Ishizaka, 1967, 1968; Ishikawa et al., 1969) identified and isolated immunoglobulins from the human atopic serum, which was classified to be class IgE. Purified IgE from the serum of an allergic individual indicated tremendous capability to induce P-K reaction. This activity was leveled by specific anti-IgE antibodies (Ishizaka and Ishizaka, 1967).

The most important but not always the most advantageous function of IgE is its capacity to sensitize homologous tissues and under certain conditions heterologous tissues of the related species (Prouvost-Danon et al., 1975; Wyczolkowska and Maslinski, 1976). The other names for IgE are: Homocytotropic Antibody and Skin Sensitizing Antibody. Human-like IgE was discovered in monkeys, (Ishizaka et al., 1969). rabbits, (Ishizaka et al., 1970a), rats (Frick and Pickart, 1970) and guinea pigs (Margni and Hajos, 1973a and b). IgE, produced by the plasma cells, can circulate in the serum or can be bonded to the affected cells. The effector cells for IgE are, the mast cells in the tissues of the respiratory and digestive tracts, skin; and the basophile cells in the serum (Ishizaka and Newcomb, 1970, Ishizaka et al., 1970). The level of IgE in serum of the healthy individual is .1 - .4 μ g/ml (Johanson, 1967). However an increased level of IgE in the serum does not necessarily result in clinical symptoms.

On the surface of the effector cells there are special receptor sites for IgE. The surface localization of IgE was shown using immunofluorescence (Hubscher et al., 1970) and autoradiography (Ishizaka and Ishizaka, 1971). IgE's are attached to the cell surface by means of the fragment Fc (Stanwood et al., 1968, Stanworth, 1970, 1971, Ishizaka et al., 1970a and b), which is characteristic for the immunoglobulin class E and is indispensable in the sensitizing process.

Other fragments of IgE, such as Fab, serve to bind it to the antigen and are uniquely antigen specific. One antigen molecule binds to two or more IgE molecules. Besides IgE there are other types of immunoglobulin in the serum of the asthma patients; mainly IgG (Bryant et al., 1973). There is no precise understanding of the role of the IgG in the allergic processes, in particular it is not certain if they do possess "reaginic" activity. It was shown that they exist on the basophile surface, but the concentration of the marked anti - IgG needed to detect the surface localization had to be about 100 times higher than the

reported anti-IgE concentration. (Ishizaka et al., 1972a). There is evidence showing that IgG has a regulatory effect on the level of IgE. Tada (Tada and Okumra, 1971), after administering IgG to an allergic rat, notice a decrease in IgE to 1/10 of the initial level after 2 days. It is known that for hay fever patients there is parallelism in the levels of IgE and IgG during the periods of severe clinical symptoms. After the desensitizing period, the IgG level is still increasing but IgE level drops. Although more researchers are devoting their time to establish the relationship between IgG and IgE and their participation in the allergic processes, at present all considerations are very speculative.

Mediators of an anaphylactic reaction

The binding of IgE attached to the surface of an effector cell to its specific antigen initiates the release of mediators of the allergic reaction. Through the years various biologically active substances were thought to be the mediators. In light of the latest studies there are three main mediators for the anaphylactic reaction: histamine (Bartosch et al., 1932, Brocklehurst, 1960, Dale and Laidlaw, 1910, Ishizaka et al., 1969, 1972, Kaliner and Austen 1974, Kaliner et al., 1972, Orange et al., 1971a, 1970, Schild 1939). SRS-A- (Slow Reacting Substance of Anaphylaxis) (Brocklehurst 1956, 1960; Ishizaka et al., 1972, Kellaway and Trethevie 1940, Orange et al., 1970, 1971a, 1973) and ECF-A- (Eosinophil Chemotactic Factor of Anaphylaxis) (Kay and Austen 1971a, Kay et al., Wasserman et al., 1973, 1974, 1975a and b). Lately leukocyte arginine esterase has been considered a potential mediator of allergic reactions (Newball et al., 1975).

The role of other substances known to participate in the allergic reactions such as prostaglandin, kinin, serotonin is not completely understood. The most widely accepted view is that the above substances act as modulators. It was

confirmed that mediators are released from numerous tissues during both active and passive anaphylactic reactions. Actively sensitized mediator releasing tissues are: lung tissue (Brocklehurst, 1960), nasal polyps (Kaliner et al., 1973a), leukocytes (Grand and Lichtenstein 1974, Dichtenstein and Osler 1964, Dichtenstein 1968). Passively sensitized tissues are: lung tissues (Parish 1967, Sheard and Killinback 1967), mast cells in monkeys (Ishizaka et al., 1977⁷²), and many others. Studies pertaining to the release of the mediators have been performed with numerous tissues and various kinds of cells but the majority deal with lung tissue, asthma being the major problem of allergology.

There is considerable agreement between the results of experiments performed on human and animal lung tissues. This is of great advantage since the range of experiments on humans is rather limited.

Now we will present a short characterization of the main mediators for the allergic reactions. Histamine (Stone et al., 1955; Uvnas et al., 1970) and ECF-A (Wasserman et al., 1973) is always present in the granules of the mast cells or basophiles, however, the SRS-A is formed as a result of binding of antigen with antibody (Stechchulte et al., 1967).

Histamine

Over the years various substances were considered to be mediators of the anaphylactic reaction but only the histamine survived the test of time and improved scientific methods.

The first reports on the histamine came from the beginning of the 20th century (Dale and Laidlow, 1910). The correlation with allergic diseases was based on the simulation of allergy symptoms by administering histamine exogenously (Dale and Laidlow, 1911). Histamine is produced and stored mostly in the granules of the mast cells. It forms a complex with the protein and heparin. It was the observation of the simultaneous release of the histamine and heparin from a dogs liver during aphylactic shock, that suggested the idea of localization of the histamine in the mast cells.

(Riley and West 1953, Rocha e Silva et al, 1947). Histamine also exists in the basophiles, and blood platelets. (This is so called beyond mast cell histamine pool). Histamine is formed from the L-histidine, the only amino acid containing the iminazole ring. This is achieved through decarboxylation with histidine specific decarboxylase (EC 4. 1.1 . 2.2) (Schayer 1956a, 1961, Schayer and Ganley 1961a, Hakanson 1964, Mackay et al, 1961) and with another decarboxylase having a wider "spectrum" of action, embracing all the aromatic amino acids (Lovenberg 1962). The latter is characterized by a reduced affinity toward histidine, but because of its abundance could also be responsible for the formation of the histamine. The histidine decarboxylase is an induced enzyme, whose activity varies widely under the influence of the external stimuli (Schayer, 1960, 1969d). The tissues are not capable of synthesizing iminazole ring and it has to be supplied externally. (Ames, 1955, Schoenhermer, et al, 1939).

The histamine is broken down by oxydation deaminosis and by methylation. The oxydation route is particularly active in those organs which transport large quantities of substances (Zeller, 1963) such as mucous membrane of the stomach (Kim et al, 1969), kidneys (Lindahl et al, 1957), liver (Shore and Cohn, 1960). The histaminase is the enzyme which acts as a catalyst for the inactivation of the histamine. There is ample data concerning histaminase activity in the blood serum during aphylactic shock. First observations of its activity were made in rabbits (Rose and Leger, 1952), rats (Lode et al, 1967) and in guinea pigs (Logan, 1961). It seems that histaminase activity is regulated by the histamine released during shock and not by the circulating histamine level (Cody et al, 1963). Breaking down of the histamine via methylation was discovered by Schayer (1952, 1953, 1956). The participating enzyme is imidazole-methylotransferase (E C 2.1.1.8). The main effect of the histamine in allergic reactions is related to its ability to cause the spasms of the smooth muscles of the bronchi (asthma, anaphylactic shock), large blood vessels and in particular vein valves,

which leads to an increased flow in the vessels. This very short description by no means exhausts the topic, which is treated in many publications. Those interested may refer to a very extensive review by Maslinski (1975a and b).

SRS-A

SRS-A is formed in the lungs as a result of immunological stimulation. It is released by specific antigen or by phospholipase A. SRS-A was discovered by Kellaway and Trethewie in 1940 in the lung of sensitized guinea pig. Brucklehurst in 1953 began new studies on the SRS-A and was able to separate SRS-A from the histamine. The chemical structure of SRS-A is not known, however, there are data indicating that it is an acid phospholipid. (Austen, 1974). It was obtained as a result of anaphylactic reactions in the mast cells in rats (Orange et al., 1970, Stechschulte et al., 1970); monkeys lungs (Ishizaka et al., 1972) and human leukocytes (Grant and Lichtenstein, 1974). SRS-A causes spasms of the smooth muscles and increases the flow capacity of the vessels (Orange and Austen, 1969). It causes spasms even in the presence of antihistamines. In the case of asthma it is responsible for the prolonged spasm of the bronchi.

ECF-A (Eosinophil Chemotactic Factor of Anaphylaxis)

ECF-A is the third main mediator of the anaphylactic reaction. It is an acid peptide with the small molecular weight. It was obtained from actively sensitized mast cells of the rat (Zasseman et al., 1974), human leukocytes (Parish, 1973), human lung (Kay and Austen, 1971a). According to the latest data, ECF-A when released, attracts eosinophils, they in turn release arylsulfatase which is responsible for phagocytose of the granules from the destroyed mast cells. This enzyme, similar to ECF-A itself (Wasserman et al, 1975a) could also inactivate SRS-A (Wasserman et al, 1975b).

The latest report was that histamine also has a strong and specific chemotactic action on eosinophils. This action, however, is significant only in a very small region of concentration and beyond this region the inhibition of

migration of eosinophils is observed (Clark, 46 al, 1975).

Arginine esterase - as a potential mediator of an allergic reaction

Newball, et al, (1975) reported the discovery of a new substance which fulfills the criteria of the mediator of an allergic reaction - arginine esterase. The kinetics of its release from the sensitized human leukocytes under the influence of the antigen is the same as for the histamine. Thus, the process is dependent on calcium ions and temperature. The release of the esterase from the cell could be anywhere from 20% to 100% of the total content in the cell. Esterase does not possess the properties of the kallikrein activator but has a kallikrein activity because it separates bradykinin from kininogen. This discovery is very important in the pathogenesis of the allergy because the arginine esterase may constitute an intermediate link between an early phase of the hypersensitivity and the kinin system.

The mediator release mechanism in the allergic reaction

The mediators of the immediate allergic reactions, with the exception of SRS-A are normally stored in the granules of metachromatic effector cells (Chakravarty et al, 1967, Mota et al, 1954, West, 1955, Wongs, et al, 1970). These processes are best known for histamine. The most thoroughly documented view seems to be that of Uvnas, et al, 1970, 1973, concerning ionic binding of histamine with the carboxyl group of the protein in the protein - heparin complex of the granules of the mast cells. An extensive review of this subject was presented by Kazimierczak (1974a).

According to the majority of researchers degranulation of the effector cells during the release of the mediators from them is an active process dependent on the metabolism, cell energy, hydrogen ions concentration, temperature and on the presence of calcium ions. (Austen et al, 1963, Mongen and Schild, 1957, 1958, 1962. Schild, 1968; Chakravarty and Sorensen, 1974; Diamant, et al, 1977; Diamant, 1975). During the anaphylactic reaction no disturbance in the cell

biochemistry, such as loss of cytoplasm or enzymes such as lactic dehydrogenase or potassium, has been observed. We conclude that the above process is not cytotoxic and does not produce irreversible disturbances in the metabolism and in the function of the effector cell. (Johnson and ^MGoran, 1969). However, none of the above mechanisms gives a total explanation of the process; it is also very difficult to explain the detailed differences between the properties of the mediator release, investigated under different conditions. It seems that all the reactions have a common course and probably differ in the initial conditions and in the details of the homeostatic control, which is responsible for the activity regulation of various stages of the reaction.

As we mentioned previously, the first stage of the mediator release from the effective cell begins with the binding of antigen with antibodies of the IgE type. The fragment Fc of the immunoglobulin is responsible for binding with the cell receptor (Stanworth, 1970, 1971, Ishizaka, et al, 1970a and b). Fragment Fab is free to form a bond with the antigen (Ishizaka, et al, 1970a, 1974; Ishizaka, 1975, Siraganian et al, 1975). According to Ishizaka, et al (1970a, 1974, 1975) and Stanworth (1970, 1971), the binding of the antigen with the antibody causes allosteric changes in the Fc fragment structure. These changes lead directly to the appearance of the so called activation sites in the effector cell membrane.

From electron microscope observations, the first visible morphological change as a result of the IgE-antigen bond is the appearance of cavities and then lesions in the cell membrane. (Sullivan, et al, 1971). As the cavities increase in size, basophil granules containing mediators, are migrating into the immediate neighborhood of the changed membrane. The joining of the cell membrane with granule membrane then results. As a result of the above process, the granules are in contact with the external environment and the exchange of histamine and possibly other mediators for the external cations takes place. This occurs

independently of whether the granules are outside the cell or remain in its interior. (Anderson, et al, 1973; Uvnas, et al, 1970).

The mechanism for the active degranulation of the effector cells is not known. It is generally believed that the motion of the hydrophilic parts in the cell membrane and the change in polarization (characteristic changes in appearance of the activation sites in the membrane) caused by the IgE-antigen bond, change the membrane properties so as to make it more permeable to certain ions (Bach, 1974). Studies by Foreman and Mongar (1972, 1973b, 1975a) and Diamant, et al (1974, 1975) lead us to believe that the most important are calcium ions, similarly as in the other secretion processes. (Douglas, 1958). Therefore, one of the most probable changes in the cell membrane, resulting from the antigen-antibody reaction could be the transient increase of its permeability for the calcium ions (Diamant, et al, 1974; Foreman, et al, 1973b; Foreman and Gomperts, 1975a; Grosman and Diamant, 1974). The increase of the ion concentration would then stimulate the beginning of the whole sequence of biochemical reactions, leading to the release of the allergy mediators. There are many proofs of this theory, the most important of which are: capture of the calcium ions by the sensitized mast cells under the influence of the antigen (Foreman, et al, 1973a, 1975c), the release of the histamine by the calcium ionophores (Cochrane and Douglas, 1974, Foreman, et al, 1973b; Diamant and Patton 1975), e.g. substances which selectively increase the permeability of the cell membrane for the calcium ions (Pressman, et al, 1968; Reed and Lardy, 1972) and also the histamine release when calcium ions are injected directly into the mast cell (Kanno, et al, 1973)

Even though the scarcity of data does not permit the precise determination of the site of the calcium ion action during the mediator release, the increase of the histamine release by phospholipids (Mongar and Svec, 1972), a part of the mast cell membrane (Mongar, et al, 1973) which has great affinity for binding

calcium (Hauser and Dawson, 1967; Foreman and Mongar, 1973a) suggests the functional relationship between calcium ions and cell membrane or related structures (Lagunoff 1972, 1973; Orr, et al, 1972). The theory of the role of the mast cell membrane in the secretion of the mediators, which are ion dependent, is supported by the fact that some substances inhibiting depolarization of the membrane (which is the prevention of the entrance of Ca^{++} ions into the cell interior) also inhibit histamine release (Kazimierczak and Maślinski, 1975a and b, Kazimierczak, et al, 1976).

Based on the above considerations and on their own observations, Foreman, et al (1975a, 1976) proposed a model to explain the secretion of histamine from mast cells with calcium ion participation, and cyclic AMP acting as an inhibitor (this is different from the Rasmussen model (1970) where both calcium and AMP activate the secretion). The main assumption of the above scheme is the existence of a membrane unit common to all selectively acting stimuli. This unit was named, "operational unit". Its activation starts off two independent processes:

1. Opening of the "channels" in the membrane for the calcium.
2. Transient decrease of cyclic AMP level in the cell, as a result of its action upon the cyclase-phosphodiesterase system. The following increase in the intracellular c AMP is an element of the cell homeostat and modulates the secretion process, so that the further entrance of calcium ions is prevented by the closing of the calcium "channels".

The precise nature of the calcium "channels" and of the "operational unit" is unknown, however, phosphatidiloserin experiments (Mongar, et al, 1973) strongly support the notion that this phospholipid functions because of the increased transport of Ca^{++} from the mast cell membrane and it is possible that it constitutes the part of the Physiological system which transports the calcium under the influence of specific stimuli. The "operational unit" can be thought of as

a part of the cell membrane, which when activated by a single stimulus, is not sensitive to the action of other stimulus. The operational unit is connected with the membrane functionally - by phosphodiesterase, adenylyl cyclase or by the combination of both enzymes. There is need for direct evidence of reactions leading to an increase in the concentration of Ca^{++} and as a further consequence to the mediator release. Indirect evidence points out that the earliest phenomenon is the activation of proesterase of the chymotrypsin type, which is an enzyme associated with the membrane, into serine esterase (Kaliner and Austen, 1973). Most probably, the serine esterase is activating phospholipase A, which is another membrane enzyme, to its active state (Bach, 1974). The phospholipase A has three partially independent functions.

1. It transforms the membrane phosphatides with a layered structure into the liposphatides with a granular structure, which increases their viscosity and is favorable to the formation of a stronger bond between the cell and the granule membranes. (Lowell and Lucy, 1969).

2. It inhibits adenylyl cyclase, by cutting off a specific phospholipid from the enzyme complex: breaking off of the phospholipid causing separation of the receptor part from the rest of the enzyme, thus prohibiting activation of the adenylyl cyclase. Those "broken off" phospholipids, when administered externally, reproduce cyclase activity (Levey, 1971a and b).

3. It inhibits adenosinetriphosphase (ATP) activity which is dependent on the so-called "calcium pump" (Wins and Schoffeniels, 1966).

As mentioned previously, the role of the cyclic nucleotides is on one hand to provide homeostatic control of the calcium transport into the cell and on the other hand it activates protein kinase. The kinase activation leads to the phosphorylation of one or more elements from the skeleton complex of the cell, those being microtubuls, microfilaments and granules (Rasmussen, 1970).

As a result of phosphorylation, the complex insensitive to Ca^{++} becomes sensitive and the granules start moving toward the cell surface. This reaction ends the energy dependent phase of the mediator release and only now when membranes of the mast cell and the granule are joined, does the ion exchange between mediators as the granules and Na^+ ions take place.

The basic elements of the mechanism leading to the mediator release are presented according to Kaliner and Austen (1974) on Fig. 1.

The data on the participation of structural elements of the cell, such as microfilaments or microtubuli in the mediator secretion process, as opposed to their role in other secretion processes are very controversial. The evidence is based on observations that colchicine inhibits the function of the microtubuli and that cytochalasin (which block microfilament activity) both inhibit the histamine release. (Orr, et al, 1972, Gillespie, et al, 1968, Levy and Carlton, 1969). However, in the light of the data on cytochalasin inhibiting glucose transport into the cell (Douglas and ~~Lieda~~^{Ueda}, 1973, ~~Lieda~~^H Yaslam, et al, 1975; Mizel and Wilson, 1972) and the fact that colchicine unspecifically blocks the degranulation process of the mast cells (~~Orr~~^{Orr}, et al, 1972), further investigations are required to confirm the role of the above elements in the mediator secretion.

The role of the cyclic nucleotides in the mediator release

In 1958, Sutherland discovered a factor, participating in the normal control of the splitting of the liver glycogen. In the following years c AMP turned out to be a regulating factor for a great many biochemical reactions.

Cyclic AMP is defined as a messenger. It is the intracellular mediator of the hormonal actions and biologically active substances. It is formed from ATP in the course of the reaction catalysed by the membrane enzyme - adenylyl cyclase (A), and is split by the cytoplasmatic enzyme - phosphodiesterase (PDE). Numerous hormones have an ability to activate AC, for instance, adrenaline, noradrenaline,

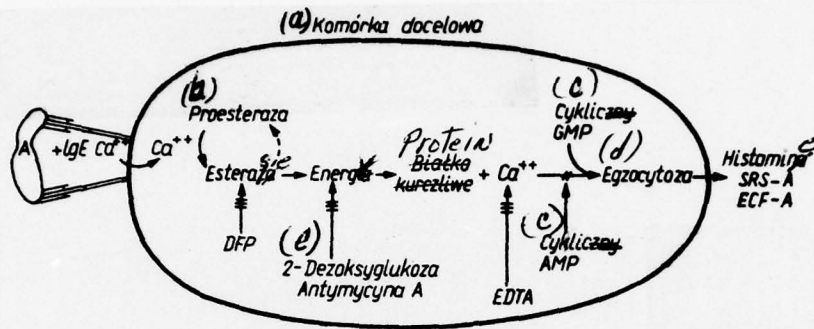


Figure 1. Main phases of the biochemical reaction leading to the release of the anaphylactic mediators. Inhibitors, active during the various stages of the reaction are presented. (According to Kaliner Austen, 1974). Key: (a) Effector Cell, (b) Proesterase, (c) Cyclic, (d) Exocytose, (e) desoxyglucose anti-mycin A.

glucagon, vasopressin, estrogen, histamine, etc. These hormones stimulate cyclase in the organs which produce them and that is why there is a long list of the effects of c AMP. The enzyme which splits c AMP, PDE is not the same in various tissues. Even in the same tissues there might be different PDE's. Their common property is an ability to produce 5^1 AMP. PDE was found in human and monkey tissues (Williams, et al, 1969, 1971), and two kinds of this enzyme were found in the lung of guinea pigs. (Hitchock, et al, 1972).

In 1936 Schild showed that adrenaline blocks histamine release during anaphylactic shock. For obvious reasons, nobody was correlating it with c AMP and its influence on the release of the mediators of anaphylactic reactions. It was as late as 1968, when Lichtenstein and Margolis found that β -adrenergic substances and methyloxantines act very strongly to prevent or inhibit (depending on the concentration), histamine release, under the influence of a specific antigen from the sensitized human leukocytes. This work started the whole series of investigations on the inhibiting influence of sympatheticomimetic amines and methyloxantines on the mediator release. It was shown that inhibition is present in actively and passively sensitized human and monkey lungs (Assem and Schild, 1969; Ishizaka, et al, 1971) and in the peritoneal mast cells of rats (Assem and Richtor, 1971; Assem and Schild, 1971). The kinetic dependance between the increase in the c AMP level and the inhibition of the release of the mediators of the anaphylactic reaction was established. The inhibition was caused by the catechol amines and methyloxantine (Lovenberg, et al, 1962, Orange, et al, 1971b and c). →

← The strengths of the inhibiting actions can be arranged as follows:

isoprenaline > adrenaline > noradrenaline, the β -receptor stimulating activity of these substances can be similarly displayed. ^{New paragraph} The inhibiting strengths for methyloxantines is as follows: theophylline > ~~caffeine~~ > theobromine, the action of the catechol amines in this case, is to stimulate β -receptors which activates in turn adenylyl cyclase and increases the level of c AMP. Methyloxantines, however, a very strong PDE inhibitor (Butcher and Sutherland, 1967, Sutherland and Rall,

1958), will increase c AMP level and will block the mediator release. The blocking action of the catechol amines in the lungs is nulled by the propranolol which suggested the participation of β -receptors in the process of mediator release. It is very possible that catechol amines play a regulating physiological function in the mediator release process. According to Assem and Schild (1969) adrenaline causes significant blocking of the anaphylactic process when its concentration is the same as in the normal blood serum (10^{-9} M). The data presented above supports the theory of Szentivanyi, (1968) on the abnormality of the β -receptors among asthma patients.

The evidence for the increased c AMP level due to the action of the catechole amines and methyloxantines during the anaphylactic reaction is the synergism of their inhibiting action to release mediators (Lichtenstein and Margolis, 1968, Tauber, et al., 1973).

It is now generally accepted, that substances increasing the c AMP level, inhibit the release of mediators of the anaphylactic reaction. Those are as mentioned before, the agonists of β -receptors or the substances that stimulate adenyl cyclase and inhibitory PDE. A similar effect is produced by a c AMP derivative - dibutyl c AMP [Orange, et al., 1971a].

The factors decreasing the c AMP level potentialize the mediator release. Most studies on this subject were performed on peritoneal mast cells of the rat using selective histamine liberators - the substance 48/80. In the mast cells of the rat where c AMP level is normally high 48/80 causing rapid decrease in c AMP, dependent on the time and dose of the administered liberator (Gillespie, 1973). The probable agent in this case is intracellular PDE. After the incubation period of the mast cells with substances decreasing c AMP level (Carbochol, adenine, diazoxyle) the histamine release increases with 48/80. However, substances which increase the c AMP level (theophyline, prostaglandin E_1) are blocking the histamine release via the substance 48/80. (Sullivan, et al., 1974).

Possibly the role of cyclic GMP in mediator release is through the activation of microtubuli (Whitfield and MacManus, 1972)

and microfilaments (Orr, et al., 1972).

It is worthwhile noticing that the microtubuli consist of subunits, each having a molecular weight of 60 thousands. The single subunit has an ability to bind one mole of c GMP. (Rasmussen, 1970). Carbochol and other substances, acting on the cholinergic receptor, activate guanyl cyclase and thus increase c GMP level (Pasternak, 1974). The post carbochol reaction is in agreement with the role of a GMP in process of activation of microtubuli and microfilaments and confirms its participation in the mediator release process. The regulation scheme of the mediator release is presented on the Fig. 2.

The role of c AMP in the dilation of the smooth muscles

Cyclic nucleotides are of great interest, not only because of their regulatory function in mediator releasing processes from the mast cells, but also because of the role c AMP plays in the dilation of the smooth muscles. The interest is obviously generated by the main symptom of asthma - suffocation, which is caused by the constriction of the bronchial smooth muscles. It has been known for a long time that histamine provokes bronchial spasms either when it is administered externally or when it is released during antigen-antibody reaction. The substances that stimulate β -adrenergic receptors in the smooth muscles, such as adrenaline and isoproterenol, prevent spasms and induce the dilation of the bronchi (Laud, et al, 1950). At the same time the stimulation of the adenylyl cyclase increases the level of c AMP in the muscles (Bueding, et al, 1966; Triner, et al. 1970; et al, 1970; Vulliamoz, et al, 1971; Valicar and Kymie, 1971). Adrenaline dilates the bronchi of guinea-pigs when its concentration is 5×10^{-10} (Blumenthal and Brody, 1969). This is close to the antianaphylactic concentration.

The other substances, contributing to the increased c AMP level in the muscles via inhibition of the PDE activity such as papaverine (Kokovetz and Poch, 1972), and methyloxantines (Butcher and Sutherland, 1962), also dilate smooth muscles. The degree of dilation is correlated with the strength of the inhibiting activity of PDE (Dobbs and Robinson, 1968, Triner, et al, 1970). It was shown

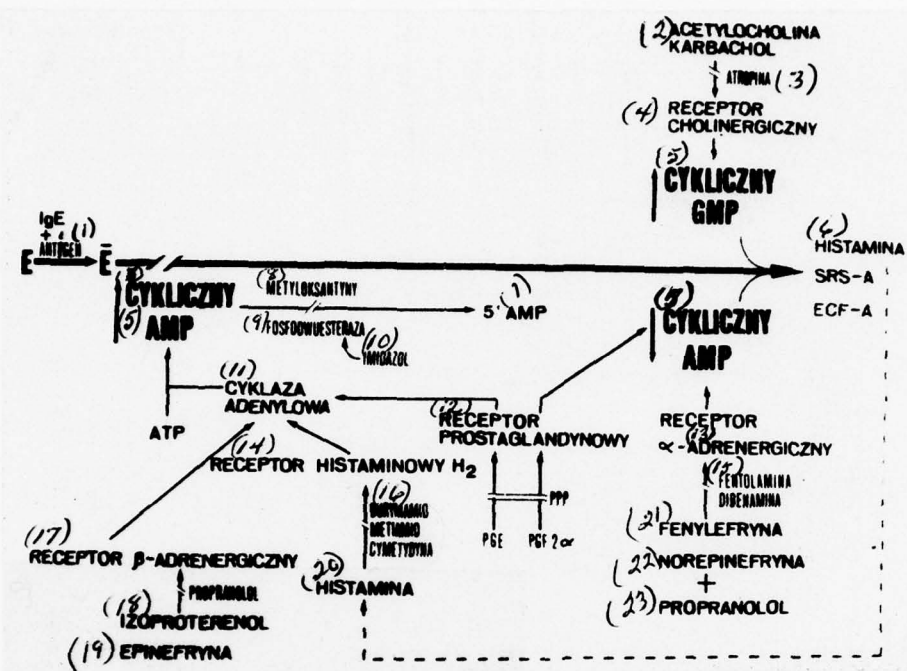


Figure 2. Regulation of the anaphylaxis mediator release via pharmacological interaction upon the system of cyclic nucleotides. (Kaliner and Austin, 1974). Key: (1) Antigen; (2) Acetylcholine carbachol; (3) Atropine; (4) Cholinergic; (5) Cyclic; (6) Histamine; (7) AMP; (8) Methylxanthines; (9) Phosphodiesterase; (10) Imidazole; (11) Adenyl Cyclase; (12) Prostaglandin Receptor; (13) Adrenergic; (14) Histamine, (15) Phentolamine Dibenamine; (16) Burimamide Metiamide Cymethidine; (17) β -Adrenergic Receptor, (18) Isoproterenol, (19) Epinephrine, (20) Histamine; (21) Phenylephrine; (22) Norepinephrine +; (23) Propranolol.

that introducing in vitro the derivative of c AMP, dibutyryl c AMP causes the dilation of the tracheal smooth muscles in the guinea pig (Moore, et al, 1968) The data presented here support to some extent the hypothesis that c AMP acts as the mediator for the dilation of the smooth muscles.

The studies on the c AMP role in muscle dilation, were mainly conducted by Andersson (Andersson, 1972, 1973, Andersson and Nilsson, 1972). His claim is that contraction and dilation of the muscle depends on the level of the mioplasmatic calcium. The role of Cyclic AMP in the muscle dilation process would consist of the exiting of the Ca^{++} bond via the microsomic fraction of the muscle. The dilation is associated with a decreased free mioplasmatic calcium level. It was shown that in the presence of the isoprenaline, the affinity for binding calcium by the microsomic fraction in the smooth muscle increases three-fold.

The methods of inhibiting the anaphylactic reaction

The cure of allergies is still a very difficult problem. Theoretically there are many possibilities to prevent their symptoms, however in practice there are few routes one can take.

Undoubtedly the most ideal but also the most difficult to practice, is the prophylactic methods, which is to isolate the allergic patient from allergenic environment.

This is an impossible task, however, since almost all of our ecosphere is "contaminated" by various allergens, the most common being the pollen of plants (Tennenbaum, 1972).

At present the most popular therapeutic actions are to inhibit the mediator releasing process and to block the tissue receptors to prevent their binding with the mediators. Very often these two methods are used together.

The notion of the receptor is rather vague and its existence is implied by the presence of agonists and specific antagonists. The first antihistamine to

block receptors was 929F. This substance prevented smooth muscle spasms of the intestines and bronchi and served as a protection against anaphylactic shock. It was created by ^(Boret) Boret. The first clinically used substance was Antergan, which had many undesirable side effects (Halpern, 1942). The derivative of the antergan, Neoantergan, proved to be less toxic and more active. Neoantergan is better known as nepyramine, receptors of the H₁ type.

It is known that antihistamine medications competing with the histamine for the tissue receptor, are not always effective. It seems that (besides the fact they also influence other mediators) one of the reasons, limiting their effectiveness is the difficulty in achieving the high concentrations needed to win the competition with the histamine released during the anaphylactic reaction. The many antihistamines synthesized during the 50's did not resist all of the pharmacological actions of the histamine. They did not prevent the action of the histamine on the release of the gastric juice, on the rats uterus, and a mammals heart (Ash and Schild, 1966, ^{Tren} ~~Tren~~burg, 1960). In 1966 Ash and Schild proposed the existence of two types of the histamine receptors. This hypothesis was confirmed by Black, et al, (1972) who after many years of trials found two inhibitory histamine receptors ^H ~~N~~₂ - burimide and metiamide (Black, et al, 1973). The same authors reported on cimetidine having the same properties, but because of its small toxicity, attractive in clinical applications (Brimblecombe, et al, 1975). From the time of the discovery of the histamine receptors N₂, the amount of data on their role has been growing rapidly (Charut and Eyre, 1975). Lichtenstein and Gillespie (1975) observed in vitro that the histamine from the cell exterior blocks the histamine release from the sensitized basophiles under the action of the antigen. This effect seems to result from the ability of histamine to increase the c AMP level (Fig. 2). Inhibitory histamine receptors N₁ do not tolerate the influence of

the histamine, however, type N_2 antihistamines, burimide and metiamide, which do not block the histamine release per se, block the inhibition of the histamine release which is caused by the histamine from the cells exterior. This suggests that N_2 receptors participate in the regulation of the response of the effector cell to the specific stimulus. The role of the N_2 receptors in the lungs is not known. It is speculated that its action is regulatory and their blockage enhances the anaphylactic reaction (Chakrin, et al, 1974).

Antihistamines are pharmacological antagonists of the histamine. The substances that dilate smooth muscles are its physiological antagonists. All the B-adrenergic receptor structures, methyloxantines and papaverine belong to the second group (Amer and McKinney, 1973). These are very useful in the cure and prevention of asthma.

There is another group of substances inhibiting anaphylactic reactions is via degranulation of the mast cells and release of the mediators from them. Besides various metabolic inhibitors, which are not considered because of their high toxicity, and besides kidney hormones and the agonists of the adrenergic B-receptors, which are quickly metabolized, there are many other substances having a similar action. Some of them are nikotinamide (Bekier, et al, 1974), zinc ions (Kazimierczak, 1974b, Kazimierczak and ^MGaslinski, 1974c, d, e) and several other substances inhibiting depolarization of the cell membrane. (Kazimierczak and Maslinski, 1975a and b, Kazimierczak, et al, 1976). The above substances can be very useful as local medications. The most useful prophylactic medication for allergies turns out to be disodium cromoglycate (^{Intal} Irtal, Lomudal). Altounyan was the first to use it in a clinical experiment on himself and found that inhalation of the disodium cromoglycate prevent a decrease in FEV₁, during an asthma attack, caused by pollen inhalation (Altounyan 1967). Later studies showed that Intal is very effective in inhibiting the release of histamine from the mast cells during anaphylactic reaction

(Orange and Austen, 1968), and from the introduction of 48/80 and phospholipase A (Orr and Cox, 1969). The preventive action of Intal was also observed after intravenous injection of the histamine liberators, 48/80 polymyxin B and dextran (Orr and Cox, 1974). The latest literature concerning Intal is very extensive and it emphasizes its effectiveness in atopic asthma. The precise mechanism of the Intal action is not known, even though its inhibiting effect on the phosphodiesterase c AMP is established (Taylor, et al, 1974a and b, Rachelefsky, et al, 1975). It is conjectured that blockage of the moderator release is achieved through the stabilization of the cell membrane. Practically this means that the membrane becomes nonpermeable to the calcium ions (Altounyan, 1975, Foreman, et al, 1975b)

The latest report is that the xanton derivative, xanton RS-7540 exhibits an antiallergic action. This is important since this substance, unlike Intal, is very easily absorbed from the digestive system and one hopes it will have wider clinical applications (Sprenkle, et al, 1975). According to the opinion of many authors, one of the most effective ways of curing the allergies is desensitizing. It is not agreed, however, whether the essence of this method is the formation of blocking bodies which can capture the allergens before they can arrive at the allergic tissues, or it is the change in the proportion of IgE formation to favor other immunoglobulins. The latter process can be realized under the constant stimulation of the cells having immunological memory with the end result being the reduction of the IgE level. (Ishizaka and Ishizaka, 1973). In the latest studies the role of cyclic nucleotides, and calcium ions in the desensitizing process is emphasized (Foreman, et al, 1976).

The next possibility to prevent allergies - inhibition of IgE antibodies synthesis - is a very complex problem and is related to the general problem of immunosuppression. The risks of this route are often higher than the risks of

allergies. Nevertheless the partial inhibition of IgE formation can be achieved using adrenal steroids (^{Berenbaum} Borenbaum, 1975). The strong side effects prevent those hormones from having a wider usage. It is possible that the synthesis of new drugs of this type, which can be administered locally without affecting the whole system, will bring about progress in the field. Preliminary studies on the Beclamethasone - new steroid drug with only a local effect are very optimistic in this respect (Mygind, et al, 1975, Gilmore, et al, 1975).

The optimal way to prevent an allergy is to block the binding of the IgE antibodies with the effector cells. This is a project for the future and there are certainly hopes that progress will be made in that area. The studies of Gorrin and Hamburger, (1975) on a peptide with a structure analogous to that of the F_c fragment of the immunoglobulin E, which can compete with it for the cell receptor, gives us some hope that progress will be made in the near future.

There is one more possibility to prevent the action of already released mediators: creation of the antibodies against them. The research on this subject is in its preliminary phase, but it might well have a practical significance in the future. By applying various sensitizing methods, many antibodies against small particles have been obtained and partly characterized, for instance [Goodfriend, et al., 1964], serotonin against bradykinin (Laborde-Burton, 1970) and histamine (Laborde-Burton, 1970; Peret and Kazimierczak, 1973).

We have presented a short review of the methods used in the cure of allergic diseases and some methods that are still at the stage of clinical experimentation. We have not considered numerous drugs which deal with and relieve symptoms. This problem is beyond the scope of this review.

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