

Early and late-phase asthmatic reactions: a hypothesis

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Why might a foreign particle, exercise or fog inhalation precipitate two asthmatic reactions? It is reasonable to suspect that asthmatic patients develop two reactions because healthy subjects may also develop two physiological responses to the same stimuli. This suggestion is supported by the observation that living things have developed adaptative systems to confront either sudden or persistent changes in the environment or within the internal milieu. The results of several studies suggest that the early phase response (EPR) usually involves cells which are normal residents of the respiratory epithelium (mast cells) and pre-formed substances (histamine), whereas cells participating in the late phase reaction (LPR) are recruited from the circulation (eosinophils, basophils and T cells). Up to now most of the studies of the EPR and LPR have been addressed to detecting a cell or metabolite abnormality. This simplistic approach would probably not improve the knowledge of the mechanisms involved in asthmatic responses. Since the presence of isolated or dual responses seems to depend on the intensity and duration of the stimuli it is reasonable to suspect that EPR and LPR are the result of an excessive adaptative response of the bodies of asthmatics to sudden and prolonged/strong stimuli, respectively.

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Allergen provocation tests usually involve exposure of the patient to increasing antigen concentrations until a bronchospastic reaction occurs. The response is usually maximal at 15 min and spontaneously resolves within 2 to 3 h. This reaction is normally referred to as "early-phase response" (EPR) because in a proportion of subjects it can be followed by a delayed phase of airway obstruction which is known as "late-phase reaction" (LPR) (2). Late responses are generally maximal at 6 to 12 h and resolve spontaneously within 24 h. Biphasic reactions have also been observed after "natural" exposure to allergens, as is occasionally the case following occupational exposure to different antigens (15). Although late reactions are usually preceded by an early response, isolated LPR may also occur. The most genuine late response usually occurs after allergic IgE-mediated hypersensitivity reactions. LPR have also been described in other circumstances including exercise (10) and fog challenges (11). Although extrapolation of data obtained from inhalation challenge to the natural manifestation of the disease may be artificial, there is evidence to suggest that late responses represent a useful clinical model for asthma.

Although there are numerous studies focused on the understanding of the cells and mediators involved in EPR and LPR, there are no hypotheses speculating on the existence of these two reactions. Why might a foreign particle, exercise or fog provoke two (early and late) asthmatic reactions?

An allergic reaction is usually considered an "excessive reaction". To some extent this concept suggests that in healthy subjects there is an adjusted, physiological response against foreign particles, while in allergic subjects the same substance elicits an uncontrollable and disproportionate reaction. When allergic mechanisms are not involved in the response, as in exercise or fog exposure, a similar excessive non-immunologically mediated response might be responsible for dual responses. It seems reasonable to suspect that allergic and non-allergic patients may develop two reactions because healthy subjects may also develop two physiological responses when they exercise or inhale a foreign substance, or after fog exposure. This suggestion is supported by the observation that human beings and, in general, all other living things have developed a variety of adaptative systems. Some of these systems are always ready to

confront sudden changes in the environment, but the human body also has mechanisms to face prolonged situations or persistent modifications of both the internal milieu and surroundings.

To confront sudden challenges, human beings have cells, hormones, metabolites, immunological mediators, nerves and neurotransmitters which may set up a rapid response in a few seconds. To accomplish this task, all cells, mechanisms and metabolites involved in immediate reactions must be permanently "on call". Cells involved in rapid responses must be at the "front line" and the substances involved must also be "pre-formed". In contrast to quick reactions, the cells involved in sustained reactions may be removed from the response site. The substances involved in the human response against prolonged challenges do not require preformation and may be synthesized when needed as mediators in the response. The way the body confronts acute and sustained stress (16) and short and prolonged exercise (3) is an example of the varied adaptive systems that have been developed by human beings.

The traditional view has been that immunologically mediated EPR involves the interaction of allergens with IgE on the surface of mast cells which are normal residents in the area of allergen contact. Mast cell activation results in the release of a wide range of pre-formed mediators, including histamine, enzymes and various chemotactic factors (eosinophils and neutrophils), as well as a variety of newly formed, cell membrane-derived mediators including PAF, peptideleukotrienes and prostaglandin D₂ (6). In contrast, cells participating in LPR are cells recruited from the circulation attracted by products released after the initial contact.

Using the nose as an *in vivo* model, Naclerio et al. (14) found differences in the pattern of mediator release in the EPR, as compared with the LPR. Although a similar rise in the levels of histamine and TAME esterase was detected during both reactions, PGD₂ concentration increased only during the early response. Since mast cells produce PDG₂ and basophils do not generate this arachidonic acid metabolite, these results suggest that the LPR may be caused in part by basophil activation.

An intense eosinophilic infiltration is also a common finding in LPR (1, 13). Tissue eosinophilic infiltration parallels a relative decrease in blood eosinophils at the time of LPR (4). Eosinophils are probably recruited as a consequence of both mast cell and T lymphocyte chemotactic factor release, such as interleukins 3 (IL-3) and 5 (IL-5) and granulocyte macrophage colony stimulating factor (GM-CSG) (17, 18, 19).

Recent studies have shown an increase in the presence of activated CD4 + T lymphocytes in the

bronchoalveolar lavage of asthmatic patients who have developed an LPR post-allergen challenge (9). Moreover, other studies have demonstrated a decrease in this T-cell subset in the peripheral blood after allergen challenge (7). These observations suggest that in addition to recruitment of basophils and eosinophils, an "active traffic" from the blood to the lung of CD4 + T lymphocytes also occurs in asthmatic patients. Since activated T lymphocytes are a potent source of GM-CSF, IL-3 and IL-5, it is conceivable that the recruitment of the cells involved in LPR is orchestrated by activated CD4 + T lymphocytes.

If the hypothesis that late reactions are mediated by basophils and eosinophils is true, it can be anticipated that as long as these cells increase in number the late reaction will occur more often. Although several studies have been carried out to assess the role of a variety of factors in the development of LPR, such as the amount of allergen inhaled, bronchial hyperresponsiveness to histamine, the size of EPR and the blood eosinophil count (5, 12), no studies have been done to evaluate the relationship between LPR and the presence of basophils and eosinophils in the respiratory mucosa. In a series of recent studies, Dahl et al. (5) demonstrated that the patients with an EPR only, could be changed to a dual-phase responder when a higher dose was given, whereas patients with an established dual-reaction lost the EPR but maintained the LPR when exposed to a lower antigen dose. Interestingly enough, when the allergen dose was increased in patients with isolated LPR, the EPR reappeared and the patients showed a dual response. Moreover, in a group of patients with EPR and no LPR after allergen challenge, when the same provocative dose of allergen was given on several consecutive days these patients developed dual responses. Altogether, these observations suggest that to some extent EPR and LPR are independent phenomena and that they occur depending on the intensity and duration of exposure. Dahl et al. (5) have suggested that differences in the cell population engaged in allergic response may account for the presence of EPR, LPR or both. Since eosinophils and basophils come from a common bone marrow progenitor it could also be possible that a sustained exposure to allergen particles may induce a parallel increase in the production of both cells (8).

Up to now, most of the studies designed to investigate the origin of EPR and LPR have been intended to detect a cellular abnormality or an excessive liberation of one or more metabolites. It has been suggested, for instance, that development of LPR may be due to a relative inability of some patients to recruit CD8 + T lymphocytes (9). This and other simplistic approaches would probably not

enable an understanding of the significance of EPR and LPR. Since the presence of isolated or dual allergic reactions depends on the intensity and duration of allergen exposure, it seems reasonable to suspect that EPR and LPR are the result of an adaptive response of the body against foreign substances, a response which in the non-asthmatic subjects is proportional to the injury.

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