Pseudo-Allergic Reactions – PAR

P.		Kallós
H.D.		Schlumberger

Helsingborg/Wuppertal

Correspondence to: Dr. Paul Kallós, Villatomtsvägen 12, S-252 34 Helsingborg (Sweden)

In susceptible individuals, therapeutic doses of drugs, well tolerated by the great majority of patients, can elicit adverse reactions, the signs and symptoms of which are identical with those of allergic diseases of any type, i.e. type I, II, III or IV according to Gell and Coombs [5]. Such side effects, which are independent of the pharmacological effect of the drug, are mostly regarded as due to drug allergy. Allergy, the state of acquired specifically altered reactivity of the organism, is characterized by (1) specificity, due to specific antibodies or specifically committed effector lymphocytes; (2) transferability from individual to individual within a species or between closely related species with antibody-containing serum or by specifically committed lymphocytes, and (3) the probability that, on renewed contact with the specific eliciting agent (allergen), signs and symptoms occur that are dependent on, and characteristic of the species, the route of administration and the type of the allergic state [4].

An example of adverse reactions to drugs is intolerance to acetylsalicylic acid (ASA) which has been known since 1902 [for a review, see Schlumberger, 12]. In about 10–20% of patients with chronic asthma, this drug elicits flushing, urticaria, angioedema, malaise, rhinitis, conjunctivitis, asthma, vomiting and hypotension; in a few cases, these symptoms culminate in fatal shock, resembling anaphylactic shock. These signs and symptoms are characteristic for type I allergic disease, mediated by IgE antibodies and mast cell activation, resulting in release of histamine, prostaglandins, leukotrienes (SRS-A) and chemotactic peptides, which are responsible for the clinical picture of the ensuing reaction. In about 40% of patients with chronic urticaria, ASA elicits flushing and hives, without respiratory symptoms.

It has been postulated as early as 1956 [6] that the adverse effect elicited by ASA in some asthmatics and urticaria patients is not an allergic reaction, but the expression of a genetically determined susceptibility for direct stimulation of mast cells by the offending drug. The main reasons for this assumption were that the adverse effect occurred often at the first intake of the drug and that it was known [15] that the reaction could be elicited by chemically and pharmacologically unrelated drugs, thus lacking specificity. Transfer experiments, performed by us in 1974 [13] have shown conclusively that asthmatics intolerant to ASA had no IgE antibodies with N-salicyloyl or N-acetyl-salicyloyl specificity, and the reactivity was not transferable. Krilis et al. [7] showed in 1981 that ASA-intolerant patients with urticaria also lack IgE antibodies with ASA specificity. All ASA intolerant patients react with the same signs and symptoms to other nonsteroidal anti-inflammatory drugs (NSAIDs), as was first demonstrated with indomethacin in 1967 [10, 16]. Many of these patients also react to therapeutic doses of

pharmacologically unrelated drugs, which in contrast to NSAIDs lack cyclooxygenase inhibitory activity [12].

Dukor, Kallós, Schlumberger and West [4] denoted such reactions, which mimic the signs and symptoms of an allergic disease but lack specificity and transfer-ability pseudo-allergic (PAR). This concept has been generally accepted and applied in many areas. The four volumes on PAR published since 1980 [4] document the importance and usefulness of the concept. Some new findings confirm this view and will be briefly discussed below.

Our asthmatic patients showing PAR to ASA and other drugs were HLA-typed by Dr. Svejgaard. At that time (1974) only the class I antigens, HLA-A, B

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and C, were known. No differences in their frequency of expression compared with that in asthmatics, who tolerated ASA, could be detected [13]. As was stressed by Schlumberger [12] the familial occurrence of asthma and ASA intolerance gave support for the hereditary nature of the condition. Mullarkey et al. [9] have recently (1986) typed 26 Caucasian patients with chronic asthma and ASA intolerance and 22 Caucasian patients with uncomplicated asthma for HLA class I and II antigens. A significant increase in HLA-DQw2 (relative risk 4.06) was found in ASA-intolerant asthmatics. According to these authors 'these findings suggest that ASA-sensitive asthma represents a disease entity unique from other forms of asthma. Presumably DQw2 or an associated genetic factor is involved in the pathogenesis of ASA sensitive asthma'. The results of Mullarkey et al. [9] give strong support to the supposition that ASA intolerance is a hereditary trait [6].

The cellular and molecular mechanisms of PAR to ASA were also unknown. Recent investigations by Ameisen et al. [1] and Capron et al. [2] clarified some aspects of the possible role of platelets in these reactions. Capron et al. [2] discovered that human platelets display a specific IgE receptor on their surface: about 6,000 receptors per cell. In healthy humans, about 10–20% platelets have such receptors, but in individuals infested with *Schistosoma mansoni* or in patients suffering from allergic asthma, the number of IgE-receptor-bearing thrombocytes is greatly enhanced and is about 50%. The IgE-bearing platelets of patients suffering from schistosomiasis 'very effectively kill parasite larvae, both in vivo and in vitro'. In in vitro experiments, the thrombocytes released a cytotoxic factor and exhibited a respiratory burst, and the free oxygen radicals produced could be demonstrated by chemiluminescence. Serum of schistosomiasis patients was able to sensitize platelets of healthy donors. Thrombocytes of asthmatics with known allergy reacted in vitro to the causative allergen with production of the cytotoxic factor and chemiluminescence. Specific IgE from the serum of such patients transferred the reactivity to thrombocytes of healthy individuals. Thereafter, the authors investigated the in vitro reactivity of platelets of 35 asthmatics intolerant to ASA and other NSAIDs. The platelets reacted on exposure to 0.6 mM ASA, 10^{-6} M indomethacin or 10^{-5} M flurbiprofen in the same way, i.e. by production of the cytotoxic factor and respiratory burst. This reactivity, however, could not be passively transferred to platelets of healthy subjects with the serum of the patients. The reactivity of the thrombocytes was not IgE-mediated. This important finding confirms the results of Schlumberger et al. [13] and characterizes the reaction as PAR. Further important observations were made by Ameisen et al. [1] and Capron et al. [2]. Sodium salicylate and salicylamide, chemically related to ASA but tolerated by ASA-intolerant asthmatics, were shown to be able to

prevent the non-IgE-mediated reactivity of platelets to ASA. IgE-dependent platelet activation, i.e. that with schistosomula or allergen, was not influenced by these compounds. In 4 ASA-intolerant asthmatics, tachyphylaxis was established by daily administration of ASA, according to the procedure devised by Stevenson et al. [14]. The platelets of these patients did not react in vitro to ASA and other NSAIDs. The molecular mechanism of the reaction is still unclear. The authors discussed the possible connection with the cyclooxygenase inhibitory capacity of NSAIDs; further investigations are necessary to clarify this matter. As was stressed by Ameisen et al. [1] and Capron et al. [2], it is presently unknown if the in vitro activation of the platelets of asthmatics intolerant to ASA by NSAIDs has pathogenic relevance. It is, however, of great importance that Capron and his coworkers have conclusively shown that PAR occurs at the cellular level.

In this connection it is of interest that Malmgren et al. [8] have recently shown that glutathione-peroxidase activity in whole blood of ASA-intolerant asthmatics is significantly lower than that of age- and sex-matched healthy individuals. Glutathione-peroxidase is one of the most powerful free radical scavengers.

D.K. Hammer and co-workers [11, and personal communication] provided recently an interesting model for the study of PAR. They showed that staphylococcal enterotoxin B (SEB) elicits in cynomolgus monkeys (*Macaca fascicularis*) in a concentration of 10^{-9} M an immediate skin reaction, clinically resembling an immediate allergic reaction, mediated by IgE. The monkeys were, however, devoid of any anti-SEB antibody. No such reaction could be elicited in BALB/c mice, Lewis or BG rats and strain 13 guinea pigs. These species were sensitized by SEB. In sensitized animals, SEB elicited skin reactions of the immediate type, the intensity of which correlated strongly with the serum IgE antibody level. Carboxy-methylation of histidine residues of SEB completely abrogated its capacity to elicit skin reactions in un-sensitized monkeys. The carboxymethylated com-

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pound, cSEB, however, was able to elicit immediate skin reactions in actively sensitized animals. Furthermore, passive transfer of rat IgE against SEB to monkey skin made the sensitized skin sites reactive to both SEB and cSEB. Electron-microscopic investigation of skin biopsies of the reaction sites to SEB from un-sensitized monkeys showed degranulation of mast cells.

Pretreatment of monkey skin sites with the histamine releaser 48/80 prevented the PAR to SEB. The reaction could also be prevented by H₁-receptor antagonists (e.g. diphenhydramine) and by a fivefold molar excess of cSEB. The immediate skin reaction to SEB in cynomolgus monkeys is thus a typical PAR, species specific and due to direct mast cell activation and release of histamine and other mediators [6].

In the few years following the publication of volume 1 of the book series devoted to PAR, important new facts have been revealed, which confirm the validity of the PAR concept. In his review of the PAR volumes, Coombs [3] wrote: 'They will undoubtedly be considered a landmark in establishing recognition and proper categorization of a series of clinical presentations and phenomena closely mimicking truly allergic reactions, but lacking the essential involvement of antibodies or allergized cells.' We hope that the PAR concept will continue to stimulate basic and clinical research.

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