Acta Paediatrica Hungarica, 25 (1—2), pp. 75—79 (1984)

Mediators in the asthmatic child

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Prostaglandins (PGF) are known to occur in premature babies with hyaline membrane disease and so the levels of PGE during growth have been investigated. The levels are lower in children than in adults; but this fact cannot explain the high resistance to air flow in infants.

The release of mediators has been shown in children and in adults. Release of histamine from circulating basophils occurs when the suspected allergenic extract is mixed with the blood of the asthmatic child. Other mediators have not been found in young children.

Cutaneous tests and respiratory challenges demonstrate indirectly the action of mediators in children, but not in infants. Between 5 and 15 years of age, the frequency and type of response to these tests are not significantly different. One may assume that, at least within these age limits, release of mediators is similar qualitatively.

Information is scarce concerning the mediators in asthmatic children except for prostaglandins E and F which have been studied with respect to growth [16, 20] and development of the bronchopulmonary system. The lack of information is deplorable.

Indeed, histological studies have demonstrated differences according to age in the structures which could respond to these mediators, by the way of adequate receptors. These differences may explain some clinical observations and the characteristics of ventilatory obstruction in infants and young children. For example, the cartilagineous structures which partly ensure the rigidity of the bronchial wall, are relatively small in the newborn compared to the adult [28]. Conversely, the mucous glands are rela--ively more developed and larger in infants and young children than in adults [15, 26]; they are also larger in children with recurrent respiratory infections than in adults with chronic bronchitis [15]. Up to 8 to 10 years of age, smooth muscles are relatively less developed in the wall of the small peripheral bronchi [15].

Ventilatory obstruction in infants is mostly due to secretions and not to spasm of the smooth muscles. But the mediators are not known and the blood histamine level during growth is not known either. In symptom-free asthmatic children, the level is within the values observed in adults [24]. Its value during ventilatory obstruction has not been studied. Neither is known the behaviour during growth of the slow reactive substances of anaphylaxis, the leucotriens and serotonin, i. e. the mediators of the type I

anaphylactic reaction. Prostaglandins (PG) have been investigated in newborns before and after treatment of open ductus arteriosus. The levels of PGE and PGF or of their metabolites are similar in full and preterm babies [16]; but in some of the latter, whose ductus is open and who show signs of heart failure, the levels of PG are high and do not decrease after ligation of the duct [13]. In hyaline membrane disease the level of PGF is augmented so that this could partly explain the vasoconstriction and the relative hypoperfusion of the lung [17]. In cord blood, the level of PGE is significantly but transitorily higher than in the adult; at two days after birth it is lower than in the adult but will increase during growth [27]. If it is assumed that PGE induced an increase in cAMP by stimulating adenylcyclase, one might suppose that relaxation of the smooth muscles of the bronchi and of the vessels would be slighter in infants and young children than in adults. The caliber of the bronchi would also be relatively smaller in infants than in adults. Indeed, Doershuk et al [2, 3] have demonstrated that during the first two years of life conductance of the airways, i. e. the reciprocal value of resistance, $Ge_{aw} = 1/R_{aw}$, increases slower than in the next years. But according to these authors who measured the total thoracic gas volumen by body-plethysmography, growth of the lung volume was also slower during the first 9 to 12 months of life. Morover, these measurements have been performed with a face-mask and the value of resistance included the resistance opposed to the airflow by the nose and the pharynx, i. e. 30 to 50% of the total resistance in infants [10, 23] like in adults [14]; but in the latter the nose is excluded, the subject breathing through a mouth-piece during measurement of the resistance. Thus it has not been demonstrated that a low level of PGE could explain a higher tonus of the bronchial smooth muscles and the high resistance to the airflow observed in infants.

Moreover, in vitro, the diameter of the small bronchi is relatively smaller in infants than in adults. The resistance to the airflow of small airways should be 80% of the sum of the resistance in infants and only 10% in adults [7]. As already mentioned, the quantity of smooth muscles being comparatively smaller in infants, the efficiency of mediators during ventilatory obstruction should be less marked, except if it is assumed that the receptors are more numerous.

Finally, from the functional point of view in the infant with obstructive respiratory disease, contraction of the smooth muscles does not seem to be the prominent cause of obstruction. Indeed, except in some few cases, sympathicomimetic drugs are not efficient before 18 to 24 months of age, as has been shown for aerosolized salbutamol [11], isoprenaline [22] and adrenaline [12] as well as parenteral terbutaline [19].

A parasympathicolytic drug, ipratropium, in aerosol could decrease the tonus of the smooth muscles [6] mostly of the large bronchi. Indeed,

the resistance to the air flow decreased significantly after inhalation of ipratropium but the total thoracic gas volume was still higher than normal in these patients and the lung was hyperinflated, the small airways having been still partially obstructed. As far as we know, parenteral parasympathicolytics have not been investigated in infants. Owing to the hypersecretion observed during ventilatory obstruction in infants, such studies might be dangerous except if the parasympathicolytic drug influenced the quality and viscosity of the mucus.

Except PGE, mediators are poorly known in infants and young children, but their presence has been demonstrated indirectly. Specific IgE has been revealed by the radio-allergo--sorbent-test (RAST) and one may assume that basophils with IgE are circulating. In some infants and young children, the total IgE level is high but no specific IgE is shown by the RAST: it will appear later on during growth [1, 4, 9].

Histamine release from the basophils has been shown by the so-called "allergic test on total blood" (ATTB) [25], the suspected allergen being faced to these leukocytes. But only the released histamine is measured and other mediators of the type I and the type III reaction have not been investigated. Sensitized mastocytes which may release mediators have been shown to occur in the skin, the respiratory and the gastrointestinal tract.

Positive cutaneous reactions after intradermal injection of the allergen were less frequently observed in the young than in the older child, a fact which is not well understood. As a matter of fact it is difficult to inject the allergen into the dermal tissue of infants and young children: it will spread out in the subcutaneous tissue. Moreover, the number of sensitized mastocytes in the skin is very small, even if the IgE level in the blood is relatively high.

According to our experience, the number of ventilatory obstructions observed after the inhalation of allergens dispersed in an aerosol was independent of age between 5 and 15 years [18] namely when house dust allergen is inhaled. The respective frequencies of the immediate and delayed (6 to 8 h after the respiratory challenge) positive reactions are similar in this age group. One may thus assume that the mechanism and the mediators involved in these reactions are, at least qualilatively, similar, irrespective of the patient's age. No information is, however, available concerning these reactions in infants and children less than 5 years old.

Receptors to histamine, i. e. one of the mediators, have been shown to occur in the bronchopulmonary system of children more than five years old. During the inhalation of aerosolized histamine, in most asthmatic patients a sudden increase of pulmonary flow resistance and a fall of dynamic lung compliance is observed. In young children an increase in pulmonary flow resistance, measured by the intraoesophageal catheter method, is due to a reduction of the calibre of

both large and small airways; at least in vitro, their respective resistances to the airflow are similar [7]. In older children and in adolescents, the resistance is influenced mostly by the calibre of the large airways. It may be assumed that an obstruction of these bronchi provoked by histamine inhalation is due to the contraction of their smooth muscles, the parasympathicomimetic way being reflectorily activated via the stimulated intrabronchial receptors.

The fall in dynamic lung compliance, i. e. the ratio between the change in lung volume and the change in intraoesophageal pressure, both being measured from the start to the end of inspiration, is due to a ventilatory asynchronism which appears when the small airways are partially obstructed [21]. Such a sudden fall of the lung compliance is observed in asthmatic children after the inhalation of a significantly lower dose of histamine than the dose provoking a flushing of the face and headache in non-asthmatic children [5].

It must be stressed that the simultaneous measurement of the lung volume change and of the gas flow in the mouth during a forced expiration will not demonstrate the obstruction of the small airways during histamine inhalation [8]. In 180 asthmatic children we observed an obstruction of both the large and the small airways, the asthma syndrome being mostly due to allergic or infectious factors. In these "infectious" asthmatic children, however, who do not respond to allergenic respiratory challenge, very low thresholds of response to histamine inhalation are less frequent than in the "allergic" asthmatic children who respond to allergenic respiratory challenge. Still, the distribution of the thresholds and their mean is similar in both groups of patients. These observations demonstrate that the response to an inhaled allergenic extract is a specific one: the threshold of the response to histamine may be very low but no obstruction is observed when an allergenic extract is inhaled by the patients.

Finally, the fall of dynamic compliance during these inhalations demonstrated that mediators are released in the small airways. More detailed analyses of these observations have to be performed but at the first approach it appears that in some patients the increase of total pulmonary flow resistance and obstruction of the large airways is observed early during the respiratory challenge. It might be assumed that non-specific receptors in the large airways are stimulated, but this hypothesis cannot be accepted. Indeed, when the same patient is inhaling different allergenic extracts, the challenge is not always positive. In other patients, the sudden fall of lung compliance and obstruction of the small airways appear before the increase of pulmonary flow resistance. One has to assume the presence of mastocytes with specific reagins on their outer surface in the submucosa of the small airways, and that they are releasing mediators which have not been identified reliably.

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Received 5 July 1983

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