

The Role of Various Factors in the Ontopathogeny of Respiratory Disorders: Focusing on Glucocorticoids

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Abstract

This article presents a mini-review describing a contribution of various agents, including stress, malnutrition and hypoxia, smoking and air pollution, respiratory infections and disturbances of immune maturation, to ontopathogeny of disorders of the lungs and airways, focusing especially on the role of glucocorticoids.

Keywords: *Glucocorticoids; Ontogeny; Perinatal Development*

The ontopathogeny is a term describing pathogeny along the whole ontogeny, beginning from pre- and postnatal development till adult state and continuing to intermediate age categories and even senescence. In this regard, we should outline that there exists certain interspecies correspondence in the stages of pulmonary development, with the last stage of alveolar formation being perinatal in humans and exclusively postnatal in rats [1], thus strengthening justification of the use of neonatal rats as experimental model of premature human newborns [2].

The role of glucocorticoids in perinatal and early postnatal treatment of respiratory disorders, as related to their ontopathogeny

The studies of various authors have shown that in perinatal period the glucocorticoids (GC), including dexamethasone, interfere with pulmonary development exactly in the stage of alveolar formation [3,4] by decreasing their number and the interface of air-blood gas exchange, therefore premature infants with bronchopulmonary dysplasia, when treated with GC, are saved from major lesions, but subsequently present alterations of pulmonary structure, with possible long-term sequelae [5].

If GC are used at the end of pregnancy with the aim of acceleration of fetal lung maturation, their unwanted effects will be more probable in the cases of multiple-dose prolonged GC use, that is not well accepted but unfortunately, takes place all over the world, including Brazil [6].

By the way, there exist only scarce data about the impact of perinatal GC treatment on the lungs and airways in the long term. However, GC are widely used also for treating respiratory diseases, especially bronchial asthma, in pediatrics, therefore, on our opinion, very significant results were obtained in newborn rabbits treated with injected dexamethasone or inhaled budesonide, describing pulmonary alterations similar to those in emphysema [7], what lead to the authors' proposal to be more careful in the use of systemic and even inhaled GC during infantile period, choosing always the least possible dose with minimal number of applications, during rather short period [8].

In spite of the necessity of precautions with perinatal GC treatment, there occur some situations that clearly show the advantages of such treatment. For example, asthmatic women without any treatment during pregnancy will have elevated risk of offspring with low birth weight, at least of female gender, whereas the use of inhaled GC allows for the prevention of this unwanted impact [9]. On the other hand, not treated bronchial asthma may result in retarded somatic growth in children, an effect similar to that of systemic or inhaled GC, therefore only the management of such treatment by highly prepared health professionals can bring satisfactory outcomes [8,10,11].

The contribution of various other factors to perinatal and early postnatal origins of respiratory diseases

In studies of the group of David Barker and some other authors, the principal attention was attracted to the consequences of malnutrition and hypoxia, provoking intrauterine growth retardation and low birth weight, with subsequent elevated risk of some respiratory disorders, especially bronchial asthma and chronic obstructive pulmonary disease already in adult state and even in senescence [12]. However, not all studies confirm this relationship [13].

Among other adverse factors, the smoking in pregnancy and lactation was mentioned as the factor causing intra- and extrauterine growth retardation, as well as altering the development of pulmonary structure and function by means of nicotine exposure [14]. Finally, air pollution, principally by ultrafine particulate matter of incomplete combustion of fossil fuel in diesel engines, provokes adverse changes in developing lungs and airways, predominantly in postnatal ontogeny [15,16].

Very important role in the ontopathogeny of respiratory disorders is exerted by infections of airways and maturation of immune responses soon after birth. At present it is well known that cellular immunity is regulated by Th1 cytokines, whereas humoral immunity is controlled by Th2 cytokines. During pregnancy the transition Th1→Th2 occurs, in order to prevent the rejection of fetus by cellular immunity, but at the onset of postnatal life there occurs rapid maturation of Th1 response [17], showing the necessity of certain antigenic load of viral and bacterial pathogens. This situation resulted in hygiene hypothesis, according to which exaggerated elimination of such pathogens from the environment of human newborns does not allow for the progress of Th1 response maturation, with greater tendency, therefore, to Th2 reactions, what provokes predisposition to atopy and autoimmune processes, including bronchial asthma [18].

On the other hand, the contribution of respiratory infections in early postnatal development was confirmed for exacerbations of bronchial asthma [19] that cause, along the many years, sometimes irreversible changes of airways and pulmonary structure and function, practically till the end of life in affected individual.

Here it is important to mention that endogenous GC participate in stress reactions and also cause a transition Th1→Th2 [20], what allows to explain the evidence on greater risk of bronchial asthma and some other respiratory disorders in the individuals affected by negative emotions and life events, especially in the cases of combined chronic and acute stress [21,22]. In this regard socio-economic status of children and their parents also contributes to the phenomena of programming/imprinting and embedding, the last of them occurring predominantly in postnatal development and in cumulative mode. However, on our opinion, the exaggerated use of GC in the treatment of bronchial asthma and allergic rhinitis may also be responsible for the phenomena of programming/imprinting and embedding, in this case of pharmacotoxicologic type [23].

Conclusion

In conclusion, among various factors contributing to the ontopathogeny of respiratory disorders, both endogenous and exogenous GC appear to have important roles.

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