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# Pharmacotoxicologic Mechanisms of Phylo- and Ontopathogeny: Focusing on Stress Hormones and Proteins

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**Abstract**

*A commentary is presented on the phenomena of programming / imprinting and embedding, as related to phylo- and ontopathogenic models, on the basis of participation of stress hormones and proteins, especially glucocorticoids and heat shock proteins.*

**Keywords:** *glucocorticoids, stress, ontogeny.*

## 1. Introduction

Earlier we have introduced two novel terms, "phylopathogeny" and "ontopathogeny" [1], in order to designate respectively pathogenic risk transfer in the inter-, multi- or transgenerational mode, i.e. across generations, and the establishment of etiopathogenic mechanisms along the whole ontogeny, beginning from pre- and postnatal development till adult state and thereafter, through middle age categories till senescence.

If ontopathogenic model is based entirely on the concept of Developmental Origins of Health and Disease (DOHaD), being elaborated for more than 30 years, from the end of eighties of the last century [2], phylopathogenic model is rather new, and only recently some more substantial data appeared in favour of this theoretical construct [3].

It is important to mention here that ontopathogenic model is a particular case of phylopathogenic model, since there occur essential interactions between the maternal and fetal organisms, i.e. the generations usually designated as $F_0$ and $F_1$ respectively. Whereas phylopathogeny usually concerns the disease risk transfer from at least $F_0$ to $F_2$, i.e. from grandmothers and grandfathers to grandchildren, although some authors consider as transgenerational case the pathogenic risk transfer from $F_0$ to $F_3$, i.e. across at least 3 generations (see discussion in [1]).

The aim of present commentary is to discuss briefly the role of stress hormones and proteins in the mechanisms of phylo- and ontopathogeny, both pharmacologic and toxic. We decided beforehand to use primarily our own articles published previously in Open Access journals, where the interested readers can find citations and references to original publications of other authors.

Why are both stress hormones and stress proteins important for our discussion? One reason is that glucocorticoids (GC) as principal stress hormones are widely used also in modern medicine as anti-inflammatory and immunosuppressive agents in the form of synthetic analogues. On the other hand, stress proteins and especially heat shock proteins (HSP) may be involved in pathogeny of some chronic diseases, such as metabolic disorders [4].

## 2. The Main Part

Earlier we have discussed the utilization of synthetic GC, in order to accelerate the maturation of fetal lung tissue in the cases of prematurity, with possible long-term consequences in the form of pharmacotoxicologic programming / imprinting [5]. Moreover, our bibliographic essay has clearly shown that endogenous GC may be involved in the mechanisms of pharmacotoxicologic action of various drugs of abuse, both social and illicit [6].

Finally, we have outlined the possibility of synthetic GC used in excess even to increase the mortality in patients treated by these drugs in chronic mode (see discussion in [7]). In the case

of pediatric use an important outcome of chronic GC use (e.g. for the treatment of leucemias) may be designated as pharmacotoxicological embedding that is characterized principally by cumulative mode [8].

Here we should mention that not GC per se, but their use in excess may provoke negative consequences. In order to diminish them, we have discussed previously the concomitant use of several hormonal and other agents: melatonin, neuroactive steroids, somatolactogens and related peptides, as well as some antioxidants [9-11].

What for the role of GC in phylopathogeny, only just recently the evidence appeared in this regard [3], but a lot of investigative efforts should be done yet, in order to expand this important area of research.

## 3. Conclusion

One of the main perspectives in future studies is evaluation of interactions between stress hormones and proteins, principally GC and HSP, in the pharmacotoxicologic mechanisms of phylo- and ontopathogeny. Unfortunately, till the present moment these aspects were not investigated in sufficient details.

For example, although it is already well known that GC inhibit somatic growth, especially in perinatal period [12], their effects on progenitor and stem cells are not well established yet [13]. On the other hand, in spite of reasonable explanations of GC involvement in the pathogeny of several cardiovascular and metabolic disorders [7, 14] on the basis of their growth-inhibitory actions, the influence of these potent hormonal factors on somatic growth proportionality is not well established yet [15].

In conclusion, a lot of investigations should be done, in order to deepen our understanding of the role of stress hormones and proteins in the phenomena of programming / imprinting and embedding, as referred to mechanisms of phylo- and ontopathogeny. Our previous suggestions for the necessity of broadening and expansion of endocrinology and gerontology [16] should be complemented now by interdisciplinary approach, enhanced by the use of artificial intelligence and systems biomedicine.

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