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REVIEW

The necessity of regional DOHaD centers based on programming/imprinting and embedding-like phenomena

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Abstract: A mini-review is presented for the evidence of growth-inhibitory effects of several psychoneurotropic drugs and glucocorticoids on developing animals and humans, together with our own data obtained in experimental models, as well as in epidemiologic studies confirming female predominance in morbidity caused by affective disorders and in consumption of some psychoneurotropic drugs. The emerging concepts of pharmacotoxicologic programming/imprinting and embedding are discussed, justifying the necessity of regional DOHaD centers.

Keywords: anticonvulsive drugs, benzodiazepines, glucocorticoids, ontogeny

1 Introduction

At present the paradigm of Developmental Origins of Health and Disease (DOHaD) may be considered as well established worldwide,[1] and the role of endogenous and exogenous glucocorticoids (GC) in programming/imprinting phenomena is confirmed in a number of experimental and clinical studies.[2] However, not only GC are used as pharmacotherapeutic agents in pregnancy, perinatal period and early postnatal ontogeny. In fact, psychoneurotropic (PNT) drugs constitute one of the categories with predominant use during human development, both pre- and postnatally.[3] In addition, at least some drugs of abuse and environmental toxicants may also affect body and brain growth during development.

Therefore, the presented mini-review aimed at discussing the evidence available on the effects of PNT drugs and GC on developing humans and animals, focusing on the alterations of body and organ growth, including our own data obtained in experimental models on developing rats.

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2 Enhanced vulnerability of developing mammals to drugs and environmental agents

On our opinion, the capacity to cause the programming/imprinting phenomena is not confined to exogenous GC. In fact, if to consider only the ability to alter body and organ growth, several anticonvulsive drugs and benzodiazepines are able to cause intrauterine growth restriction (IUGR), low birth weight and diminished head circumference or retarded brain growth.[3–7] This was already proved for phenobarbital, phenytoin and carbamazepine, as well as for diazepam and some other benzodiazepines, both in animals,[8–14] and in humans.[15,16] From the drugs of abuse, especially cocaine and amphetamines are the first to be suspected for provoking IUGR, low birth weight and diminished head circumference. Finally, there is some evidence on growth-inhibitory actions of polychlorinated biphenyls (PCB) in critical periods of human development,[17] probably due to their capacity to interfere with effects of thyroid hormones.[18]

There are several explanations for higher vulnerability of central nervous system (CNS) in developing mammals to adverse effects of PNT drugs.[19,20] One of them considers lower activity of hepatic metabolism of xenobiotics in perinatal period, as well as higher permeability of immature blood-brain barrier to PNT agents.[21,22] However, the main factor explaining this peculiarity of developing mammals appears to be high liposolubility of PNT drugs and corticosteroids that facilitates their passage both through placenta and blood-brain barrier.[22,23]

On the other hand, it is important that PNT drugs interact with hormones. For example, phenobarbital in-

teracts with dexamethasone in regulation of alpha1-acid glycoprotein production by hepatocytes;[24] in addition, it interferes with hepatic metabolism of sex steroids, resulting in alterations of growth hormone secretion,[25] whereas benzodiazepines provoke the diminution of the activity of hypothalamo-pituitary-adrenal axis,[26] and on the contrary, phenytoin is capable to enhance corticosterone secretion in mice.[27]

3 Our own data on the effects of glucocorticoids and psychoneurotropic drugs on developing animals

The involvement of the author in this important topic began already during the decade of nineties in the last century, when it was possible to observe greater inhibition of DNA and total protein biosynthetic rates by dexamethasone in pituitary cell cultures of neonatal rats, as compared to prepubertal and adult animals.[28] Thereafter it became possible to show sustained retardation of body and organ growth by dexamethasone administered to neonatal rats.[29]

Later on, we compared the effects of glucocorticoids and some PNT drugs on body and organ growth in rats. We have demonstrated growth-inhibitory actions of phenytoin, phenobarbital and diazepam administered neonatally to rats or later in postnatal ontogeny, however, in general, these effects were less intense and not so consistent, as compared to those of GC.[30]

One of the most interesting peculiarities discovered was growth-inhibitory action of diazepam on pituitary gland, but it is important to note that previously similar action was demonstrated already both in vivo and in vitro by another researchers.[31,32]

Finally, we were able to show the capacity of GC and some PNT drugs to diminish the extent of hydration in the organs evaluated,[33] and again the effects of GC were much more intense and consistent, as compared to PNT drugs. After Selye *et al.*,[34] we interpreted these data as one of possible mechanisms of growth inhibition provoked by these drugs, as related to cell shrinkage and apoptosis,[35] contrary to cell swelling in growth stimulation.[36]

4 Pharmacotoxicologic programming / imprinting and embedding

The term and concept of pharmacological programming was introduced by British obstetrician Helen Bayliss and her colleagues, when discussing the effects of atenolol and other beta-blockers in pregnancy.[37] More recently, we have expanded it to pharmacotoxicologic programming / imprinting and embedding.[38,39] What is the difference, as related to original concept? Primarily, not only beneficial, pharmacotherapeutic action is included, but also adverse, unfavorable and potentially toxic effects are considered. In addition, the embedding phenomena are intended as chronic, cumulative and occurring predominantly in early postnatal ontogeny, as compared to programming/imprinting events, characteristic for relatively acute and subacute influence in prenatal and perinatal periods. Of course, there may be some overlapping in these phenomena, depending on pharmacotherapeutic regimens utilized.

Why is it so important to elaborate and use these concepts? Surely, nobody is interested in promoting steroid phobia or some similar problems. However, we find as highly unwise not to note obvious adverse side effects of GC and at least some PNT drugs. Moreover, we suppose to use experimental models on laboratory animals to find out the ways of diminishing adverse side effects and consequently, pharmacotoxicologic programming / imprinting and embedding, e.g. by the use of adjunct antioxidants[40] or some antistress agents like melatonin.[41,42]

At present it is well established that epilepsy, depressive illness and other neuropsychiatric disorders, if not treated in pregnancy, are dangerous *per se* in potentially provoking adverse perinatal outcomes,[43,44] therefore it is not a question, to use or not to use PNT drugs during gestation.[14,21] Since our participation in Expert Committee on Psychopharmacology, associated with the Secretariat of Health Affairs in the Government of Brazilian state of Rio Grande do Sul (RS),[46] we were already interested in more detailed studies of PNT drugs and neuropsychiatric disorders. As a matter of fact, we were able at first to show clear-cut gender differences, with female predominance in the consumption of at least, benzodiazepines and antidepressants in North-Western region of the state of RS[47] and thereafter, in morbidity associated with affective disorders in three Brazilian states of Southern region. In addition, in a pilot study we have obtained preliminary data on substantial consumption of PNT drugs in women younger than 40 year old, what allowed us to suggest higher risk of pharmacotoxicologic programming / imprinting in this fertile female subpopulation.[38] Characteristically, the peak of morbidity caused by affective disorders takes place also in the intermediate age categories.

5 Conclusion

Surely, we are aware of the difficulties in organizing long-term prospective studies of drug surveillance in experimental models on rodents up to adult state and espe-

cially, till the senescence.[48] Really, the results of such studies are quite rare in world literature[49] .

Even the retrospective epidemiologic studies need the eminent scientists like David Barker who was lucky enough to discover the archives in Hertfordshire (UK) of the beginning 20^{th} century[1] . Therefore, we would like to propose the necessity of organizing regional DOHaD centers that could be responsible for performing epidemiologic and experimental investigations in the framework of DOHaD. Obviously enough, the principal goal remains the same: to promote better health, particularly in the groups of pregnant and lactating women, children and the elderly.

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