Archives of Oncology and Cancer Therapy

ISSN: 2638-5074

Volume 2, Issue 2, 2019, PP: 1-5

Gestational Medication and Unpredictable Cancer Development in Offspring

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Abstract

There are critical developmental periods of life (the most determining is the perinatal one), when exposure to certain hormone-like molecules can reprogram the developmental program (methylation pattern), provoking late-manifested diseases and different alterations in the endocrine or endocrine-regulated systems. This is the faulty hormonal imprinting when for example endocrine disruptors, whilst behave as functional teratogens, transform the developmental program for life. However, in the last time publications appeared showing that not only hormones or hormone-like molecules (endocrine disruptors), but non-hormone drugs also can lifelong disturb the normality of program, causing late manifested diseases [developmental origin of health and disease (DOHaD)] onthe basis of hormonal imprinting. In the present article such drugs named„medigrammers" by us, are introduced, which after gestational employment provoked late (childhood or adult) tumor formation and the possible mechanism of their effects (reprogramming) is discussed.

Keywords: *Drugs, faulty imprinting, perinatal period, developmental program, reprogramming, late effects*

After fertilization the zygote's genome contain all of the informations which are needed for the further development and also has the program by which the information can be realized. This information is coded by the DNA (genes) however, there are also epigenetic influences which determine the expression of genes for life [1]. The basic genetic information is present in each cell of the organism, equally e.g. in the liver cells or the retina however, while in the liver detoxification and bile production are taking place, the duty of retina is the visionand the function of different genes are necessary for the different functions (except the so cold household genes, the function of which is absolutely needed for all cells). This means that from the uniform gene pool different genes are working in different cells [2], and this is named gene expression. A part of genes are blocked by methylation of cytosin nucleotides, which is done by the contribution of methyl-transferase enzymes, and this is resulted in the methylation pattern of the genome. However, there is also a possibility of demethylation (done by demethylases) which is folloved by re-methylation (of the same or other the sites) by which the program (expression of genes) couldbe changed in the course of life. There are critical periods of life which not only allow reprogramming, but request it, as the perinatal (fetal, neonatal or postnatal) periods, a well as weaning and puberty. In this critical periods excess of physiological hormones can disturb the normal development of receptor-hormone connection and molecules, similar to a given hormone (other members of the hormone family, synthetic hormones, hormone-like endocrine disruptors) can develop faulty hormonal imprinting with lifelong consequences (alteration of hormone-binding capacity, inclination to diseases, manifestation of diseases, disturbances of behavior etc) in different systems of the imprinted (reprogrammed) organism which is also inherited tothe progeny generations [3]. This means that a single very low dose effect in the critical period, when the developmental window for imprinting is open,provokes lifelong sequelae, by epigenetic reprogramming. This was at first observed and named hormonal imprinting by us in the last decades of the last century [4-6] andin the

last time it can be justified by Barker's developmental origin of health and disease (DOHaD) theory and its examples [7,8] This faulty imprinting is also inherited tothe progeny generations (observed up tothe third generation in rats and up tothe 1000th generation in the unicellular model, Tetrahymena [9].

It seems to be understandable that related hormones and hormone-like molecules (e.g. endocrine disruptors) provoke faulty hormonal imprinting, as this can be deduced to a disturbed cellular memory however, in the last time publications appeared, demonstrating the imprinting-like effects of non-hormone medicaments acting in the critical periods of development and manifested in diseases in later (childhood or adult) periods of life [10,11]. This points to the especially important observations of these critical periods fromthe aspect of medication.

The cells of the immune system have a special position in the observation of faulty impinting, as the cells of it are continuously dividing establishing the possibility of reprogramming (faulty imprinting) during the whole life [12]. As the condition of immunity has a basic role in the development and progression of tumors it seems to be interesting to study the interrelations between treatment by medication in the critical early periods (gestation) and cancer development.

Selected facts on oncogenesis long time after gestational medication (on the basis of PubMed and Google)

Increased risk of brain tumor was observed after treatment (of mother) with beta-blockers, during late gestation [13].

Nitrosatable common drugs (aspirin, antihistamines, antibiotics) increased the risk of brain tumor development of offspring [14-16].

Methylation (reprogramming) of genes was associated with antibiotic use during gestation [17].

Maternal use of antibiotics, iron and nervous system drugs during pregnancy could be associated with some childhood cancer subtypes [18].

Some specific types of childhood cancers (eg. hepatic cancers) are associated with antibiotic (e.g. tetracycline) treatment during pregnancy[19].

There is an increased risk of cancer in the offspring of mothers who had antibiotic treatment during pregnancy or in the last three months before conception[20].

An increased risk of certain cancer types was associated with antibiotic treatment during gestation [21].

An increased risk of neuroblastoma was associated withdiuretics and other antihypertensives (most markedly) and also with iron, folate and vitamin supplementation.Maternal use of diuretic or neurally active drugs during pregnancy is associated with neuroblastoma [22].

Sedatives, anticonvulsant drugs or drugs forming N -nitroso derivatives enhanced neuroblastoma manifestation in the offspring [23].

In healthy populations folat intake reduces risk of cancer however fortification of folate during pregnancy increase later cancer incidence (24, 25).

Excessive folat intake during gestation promotes manifestation of tumors (26).

Discussion

Studying the data (Facts) it seems to be clear that there are certain medications (drugs) which provokes tumor-formation in the human organism far from the exposure to medicaments. If the effect would be perceptible in the time of treatment or near after it, this could be classified a direct effect of the drug, however, for months or years after exposure a memorization of the impact is needed, which permits the suspicion of developmental program reprogramming. If the provocator of this process would be a hormone, or hormone-like molecule, it could be named faulty imprinting and the lifelong effect could be easily accepted, as this was proved many times previously [10,11]. However in the present case non-hormonal (and presently not listed as oncogenic) molecules provoked the development of tumor so far from the exposure, that only targeted observation could justify the interaction between the provocator and result. Antibiotics and nitrosable drugs (among them the "ancient" aspirin) as well, as a vitamin (folic acid, B9) and antibiotics are mentioned in different (independent) studies, supporting each other. In earlier papers paracetamol was also mentioned, as provocator of later manifested non-oncogenic diseases, which does not mean that painkillers have an outstanding role for provoking late harmful effects

rather than other medicaments, but these are used more frequently, than others and their dangerous effects are more conspicuous, then that of others. Most of the studies mentioned in Facts are not systematic, only observations -which was drawn by somebodies' attention to something- and pain-killers are used more frequently, than other drugs, gestationally.There were not systematic animal experiments for clearing the oncogenic effects, only sporadic observations on human cases, what makes presumable that any effective molecule is able to provoke tumor development in a sensible critical period (open window), when the reprogramming is permitted, or requested.

Considering in certain aspects, oncogenesis requires the alteration of the developmental program, which also could be manifested in the invasion and matastatizing of cancer. This means that for the manifestation of cancer activation of faulty genes -present in the original genome- or epigenetic modifications of normal genes, are needed. Irritation by carcinogenetic agents (as e.g. benzpyrene) provokes a direct oncogenetic response however, the data in Facts contain such cases, when the development of tumor appeared far (months or years, sometimes decades) from the exposure to medicaments as a consequence of reprogramming. The molecules, in addition to their beneficial (healer) effects were different and only one characteristic was common: their ability to provoke - by gestational exposure - late tumors. In addition the provoked tumors were also different, in origin, in structure and malignity.

As these drugs act by reprogramming it could be called as a comprehensive (cohort) name, "medigrammers" and considering the tendencies in pharmacology and pharmaceutical industry their amount (and effect) will enormously growing. These drugs in the medical vulgar-tongue are not oncogenes, as this latter character is only a side-line, which -considering the long time between the exposure and manifestation- is difficultly justified, however the presence and propagation of them is warning and frightful.

In the program of a cell different genes are contributed regulating cell division and inhibiting or enhancing tumor formation. There are genes wich inhibit cell division and tumor formation, this are suppressors (most studied is p53 gene) and there are enhancers, promoting cell division. In normal case these are working as proto-oncogenes and they are programme-likely methylated (blocked), according to the function required. If a tumor suppressor gene is hypermethylated , it is blocked, permitting information transfer for cell division, similarly to the demethylation of enhancer genes [26]. If the promoter of tumor enhancer gene is over-methylated, cell division is also inhibited. In cells having normal program the effects of suppressor and enhancer genes is well-balanced however, if something disturbs this balance, their function will throw out of line, and ensure free way for malignization. As the possibilities are at least two-sided and with high probability more-sided (without exact examinations) it seems to be likely, that the effect of "medigrammers" are manysided. Moreover, the list of medigrammers (studying the list of Facts, which is only a selection) so broad, that somebody can believe that any strongly effective pharmacons (from painkillers to vitamins [e.g. folate] and antibiotics) are able to be "medigrammer", only the developmental (perinatal) period in which the effect arrived and accepted, has a decisive role.

It is very important to consider the participation of the human body in the transformation of medicaments to cancerogenic substances as it is observed in the case of putative carcinogenic nitrosamines. Similar transformations can be occured in case of other chemicals. This also points tothe difficulties in the listing of late-tumor-provoking medications.

Knowing the late-manifested dangerous sequelae as well, as the absence of systematic studies on tumorigenicity (as was done in case of direct-synchronous- oncogenesis [27]) of medigrammers (which seem to be hopeless, because of the present and continuously growing amount and variability of drugs), our standpoint could only be the avoidance of medication of pregnant women, especially in the thirdtrimester of gestation and dogging (and publishing) the traces in offspring of such mothers who got some treatments after all. Doctors can not refuse the arguments calling attention to the dangers of medication, mentioning that some medicaments are used since decades or centuries, as these molecules had not been studied from the aspect of late manifested tumors, and for example aspirin (as a salycilate) has been used since very long time (centuries ago) and its late-cancerogenic effect was unravelled only now.

The recognition of hormonal imprinting was the first observation to the memorization of perinatal effects

to late alterations in mammalian organisms. This theory was confirmed many times [28-36] and DoHaD pointed to its role in the development of human adult diseases [7,8,37]. The observations on late manifested tumors after perinatal medication call attention to the dangers of any medication during gestation which must be avoided, if possible at all.

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Citation: **György Csaba.** *Gestational Medication and Unpredictable Cancer Development in Offspring. Archives of Oncology and Cancer Therapy. 2019; 2(2): 1-5.*