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Molecular epidemiological and epigenetic examination of artifical food colourants

Doctoral (Ph.D.) thesis

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Introduction

Nutrition is a key part of our life, because the macro- and micronutrients and other food ingredients delivered with foods and drinks have a permanent impact on the physiological processes of our body, our health and our quality of life. Most chronic, non-contagious diseases have many nutrition-related indications, they even may be cumulatively in a causal relationship (obesity - tumors, diabetes, hypertension). Cancer diseases occupy a privileged place in mortality statistics. Worldwide, these diseases are responsible for 12% of 56 million deaths per year (WHO, 2017).

According to Hungarian data, if mortality for cardiovascular diseases is considered as one category, then deaths associated with malignant neoplasms are on the second place (25% of total death). When separating cardiovascular diseases (acute myocardial infarction, other ischemic heart disease, cerebrovascular disease) the number of these cases is even more evident, according to the total mortality rate. The frequency of occurrences of certain types of cancers is also increasing in Hungary. If the morbidity data of lung tumors and female breast tumors per 100,000 population are examined from 2003 to 2015, the upward incidence can be observed.

The prevalent number of patients, including the number of cancer patients registered in GPs, is constantly increasing, even if the registered patients represent only a fraction of the number of actually sick individuals (hidden morbidity). Therefore, we can conclude that we are confronted with a major pathology of public health risk.

Food industry in developed countries is constantly trying to adapt to individual consumer needs, it ideally includes continuous product quality. Moreover, it should be remembered that this can have many adverse consequences, one of these is the spread of the use of additives and the continuous growth of their use. The food industry does not want to change the "proven" production processes or production protocols from the point of view of material considerations or the intractability of the technology; even though most of them use synthetic and artificially produced additives (Szakály, 2008).

At the same time, the question arises whether these substances may have such harmful, health-damaging effects and how these effects can be detected.

One of the most commonly used additives - to influence organoleptic properties - is the group of artificial dyes (Raposa et al., 2016a).

Controversial results with artificial dyes and tumor-inducing effects are often unclear, as in most studies, these substances are studied in elemental and totally different doses. Their metabolism, their effect, their genotoxicity, their possible carcinogenic effects in different studies show different results (Poul et al., 2009; Tsuda et al., 2001).

Objectives

1. At the beginning of our investigations, it was assumed that in the case of experimental animals consuming food containing artificial dyes (separated and added together) at a given concentration (multiple doses) at the level of the metabolizing enzymes, the activity of cytochrome P450 enzyme family members (CYP1A1, CYP2E1) will be different compared to the control group, in the case of samples from many organs, supposedly proportional to dose growth, mRNA concentration increase can be observed.
2. We also assumed that in the case of genes and kinases involved in the regulation of the cell cycle (NF-κB, GADD45α, MAPK8), due to the exposure of the artificial dye as described above, a higher mRNA concentration was measured relative to the control group. Linear relationship of exposure effect is also assumed in this case.
3. During our research, we also sought to find out how the food colors interact with each other, how does consuming them together affect the abovementioned biomarkers.
4. We have assumed that the expression levels of methylation biomarkers (DNMT1, DNMT3A, DNMT3B) - in dose-dependent manner - will have significant differences in treatment groups compared to each other.
5. In addition, in comparison with generations, there are significant differences (depending on exposure) in the expression pattern of the genes involved in methylation, which demonstrates the growth in the generation (our aim was to find out the consequences of parental and grandparent nutrition).

Materials and Methods

In our investigations, we used 4-6 weeks old carcinogenic - sensitive, inbred Balb / c nude, AKR / J and CD1 mice. Male and female specimens were used in our experiments, and their selection was performed by random sampling. The animals were bred in an animal home belonging to the National Public Health Institute of PTE Medical School. The minced normal rodent food was mixed with the calculated amount of Tartrazine and Azorubine. The powder mixture was mushed with tap water, mixed, cut in pieces and then dried in a drying oven (temperature: 40 °C, drying time: 48 hours).

There are two azotic dyes in our research: we sought to examine the effect of tartrazin and azorubin on genes involved in the gene expression and methylation pattern, at mRNA level, by assaying the samples from the bodies of the experimental animals, based on the Trizoll protocol RNA was isolated and analyzed by RT-PCR.

Our experiments were carried out using the ROCHE LightCycler 480 equipped with a built-in normal PCR and a CCD camera. The software on the device was programmed as described in the kit protocol then the plate was placed in the device, the CCD camera was recorded in the correct position, then the help of the software started the reaction. The resulting fluorescence extinction was evaluated via an AD converter using a computer program. The gene expression levels are defined compared to a so-called „House keeping" gene (HPRT1) and then they were compared in each treatment.

"Short term" treatment of Balb / c nude mouse strain – according to CYP450 metabolizing enzymes

Balb / c nude mice of the age of 4 to 6 weeks, regardless of sex (male and female individuals) were examined by random sampling. The number of groups was determined in 6-6 (n = 6) according to the research type and group number, as well as the protocols of relevant foreign researches. The experimental animals were divided into 7 groups based on the treatment method. Animals ad libitum consumed tap water throughout the study. The test animals were fed for 15 days with the calculated amount of food (2g standard rodent food per day / individual) and the added colorant, and two groups were injected intraperitoneally on day 14 (dose: 20 mg

/body mass kg) with DMBA. After cervical dislocation, we took samples from each organ (liver, kidney). RNA was isolated from the organs by the Trizol protocol.

’’Long term” treatment of AKR / J mouse strain – examination of expression of genes involved in cell cycle regulation

For the second stage of our study, 4-6 weeks old AKR / J mice were selected randomly, regardless of gender (male and female individuals) by random sampling. Similarly to the first stage, the number of groups was 6 - 6 (n = 6). The experimental animals were divided into 7 groups according to the treatment method, details are given in Table 7. After the first phase, it was suggested to examine the possible effect-additions and their effects, therefore the treatment was determined accordingly. Animals ad libitum consumed tap water throughout the study.

The calculated amount of nutrition and the added colorants were given for 42 days for the test animals (2g standard rodent food per day / individual). After the treatment, on the 43rd day of the experiment, the animals were sacrificed. After cervical dislocation, samples were taken from their liver. RNA was isolated from the organs by the Trizol protocol. For a comparative analysis of our investigated groups, a control group was used.

"Multigenerational" treatment of the CD1 mouse strain – according to genes responsible for the development of methylation patterns

Our multigenerational study has been designed to examine the effects (inter-generational, trans-generational) of the treatment as described below according to genes responsible for the development of methylation patterns. In the last part of our study, we used 4-6 weeks old CD1 mice as a starting point. In order to achieve a more complete result, we separated the sexes in this case, so we examined male and female individuals within the treatment group. The number of groups included 6 female and 6 male individuals per generation (n = 12). The animals were breeded within the given treatment group to examine the possible long-term epigenetic effects of the same treatment on generations. The entire study included the treatment of 3 generations including the initial G0 generation. The experimental animals were divided into 3 groups

according to the treatment method. Due to the time required for the study, we have chosen the tartrate (examined several times before) as the exposure based on our preliminary results. The animals ad libitum consumed tap water throughout the study. 4- 6 weeks old mice of the 0th generation (G0) were fed for 42 days with the calculated amount of food (standard rodent food 2g / day / individual) and added colorant, then they were breeded. After the birth (18 - 19 days) of the inbreds, until the removal from the mothers (21 days) the parents still receive the special and control potions. After separation, cervical dislocation was performed on the G0 specimens, and samples were taken from their liver and kidney (taking into account the major localization of expression of DNA methyltransferases).

The individuals of G1 were grouped and fed int he same way as their ancestors, until they became mature (7-8 weeks old), then they were propagated and we did everything in the same way as in the case of G0 (pregnancy, continuous treatment under the secretion). In the case of G2, the method and the treatment was in the same way as G1. In each case of organ tissue samples RNS was isolated by the Trizol protocol.

Method of statistical analysis

For statistical methods, the normal distribution was tested by a single Kolmogorov-Smirnov test, Levene's F test was used to determine the scattering, followed by ANOVA test and post-hoc analyzes of variance analysis. For our calculations and analyzes: Microsoft Office Excel 2016 and SPSS 22.0 Statistics software were used. The statistical significance level was determined at $p \leq 0.05$, with a 95% confidence interval.

Results

In the case of CYP1A1 gene products, overexpression was observed at several doses as well as significant differences in the control group (liver). The highest overexpression was given by a mixture of tenfold tartrate and the common exposure of DMBA, where the significant difference compared to the control group is likely to occure due to the addiction ($p < 0.05$). Significant difference was measured at a 10-fold dose of separate exposures ($p < 0.05$), not at

single doses ($p > 0.05$). Relative gene expression from the tissue homogenate of the kidney showed similar results. However, in this case, the single and ten-fold exposure of azorubin did not induce gene expression increase in the examined gene (CYP1A1). In the kidney, ten-fold tartrazine typically produced a significant increase ($p < 0.05$), but in this organ, even with DMBA, there was no such increase in expression as DMBA itself.

In the case of CYP2E1 liver samples, each group was elevated in comparison to the aqueous control. Azorubin's exposures did not show any increase in proportion to the amount of substance. In the case of both single and tenfold doses of tartrazine, significant differences were detected ($p < 0.05$), and dose-related increases were also shown in this case.

In DMBA-treated groups, similar results were obtained as in the CYP1A1 kidney samples. In this case, the 10-fold tartrazine + DMBA-treated group showed a significant increase not only compared to the control but also in comparison with the ten-fold tartrazine exposure group. In CYP2E1 kidney samples' gene expression changes followed the proportion of the CYP1A1 kidney samples. It is important to note, it first occured in these samples that the tartrazine exposure caused a lower increase than the control group.

For colorants, it can be concluded that in the case of NF-κB, the exposure of azorubin, ten-fold tartrazine and the exposure of the two substances showed significant differences in the control group ($p < 0.05$). The results show that in the case of NF-κB, compared to the tartrazin + azorubin single exposure group, only the ten-fold exposure of tartrazine shows a higher increase. Ten-fold exposures of the same materials, we have found a dose-enhancing signal in several cases both in the common exposure and the 10-fold exposure of tartrazin. For GADD45α it can be stated that compared to the control group, one group showed only significant differences ($p > 0.05$). The possible causes of the unchanged results of GADD45α (not including single Tartrazine) and a fully normal expression pattern will be examined in the future.

For MAPK8 again tartrazin and the common exposure of the two substances showed significant differences in the control group ($p < 0.05$). Changes in the gene expression profile were also observed in addition to azorubin, which in this case, increased proportionally with the quantity of the material but did not prove to be significant ($p > 0.05$). The single-dose and ten-fold exposure of tartrazin and the common exposure of the two materials gene expression patterns showed a dose-dependent increase.

Summarizing the expression results of genes involved in methylation it can be said that there was a significant increase among the second and third generation in mRNA level, for all genes (DNMT1, DNMT3A, DNMT3B), while in the liver these changes showed up in several cases only in the comparison of G0 -G2 relations, in the case of kidney samples, this was already observed in the G0-G1 comparison, not to mention the level of „overexpression" in G2. A dose-dependent increase was confirmed between presumed generations on expression level.

It should be noted that our assumption on the generation enhancement is also justified, because with the increased amount of substance, at tenfold exposures in both the liver and in the kidneys showed significant differences between G0-G1-G2 and tendency enhancement.

Discussion

We wanted to examine the biomarkers at different points of the tumor formation process, which indirectly both in an molecular epidemiological and epigenetical affection (expressional changes in methylation pattern) can „light up" these materials' in vivo mechanisms and their role in tumor development. Additives used in the food industry, especially the dyes, means a continuous low dose exposure from an early age to our body. Genetic / epigenetic changes occurring after several years of exposure are likely to be associated with tumor development (Esteller, 2008).

There are two azotic dyes in our research: we wanted to examine the effects of tartrazin and azorubin on gene expression and on genes effection the creation of methylation patterns at mRNA level, by assaying samples from the bodies of the experimental animals, using Trizol protocol RNA was isolated and analyzed by RT-PCR.

Based on the changes in cytochrome P450 enzyme families (CYP1A1 and CYP2E1), it can be said that azorubin did not cause significant gene expression changes in the metabolizing enzymes. Accordingly, our test results further expansionin the in vivo and in vitro literature data, in which no signs of genotoxicity or carcinogenicity were found (EFSA ANS, 2009b; TemaNord, 2002). According to tartrazine there was a significant increase in gene expression and in many cases significant differences were observed. It should be noted that these differences were in our case dose-related, not to mention the interaction with the chemical carcinogen in the case of both CYP1A1 and CYP2E1.

However, it has to be noted that the comparison of DMBA treatment with ten-fold tartrazine exposure + DMBA treatment resulted in an interesting result as the level of DMBA proved to be higher, so the question may arise, whether the substance may have a high dose of chemopreventive effect in these chemical carcinogens. We are planning further investigation of this issue to decide this statement and riview our results, since no data with similar effect was found in the literature.

In the case of genes involved in cell cycle regulation, our previous results were further confirmed. The results obtained with CYP450 metabolizing enzymes were greatly influenced the expression changes in NF-κB, GADD45α, MAPK8 genes. Based on our results, the effect of azorubin itself, compared to the control group, did not have significant modifying effect on gene expression. Thus, scientific results are supported by the results of our study with no observed carcinogenic effects. (Durnev et al., 1995; EFSA ANS 2009b; Holmes et al., 1978 a; b; Gaunt et al., 1967).

Regarding the effects of Tartrazine, we can already report more significant results. Excluding the GADD45α gene (the reason for this is going to be considered in the future) a significant increase in gene expression levels was measured compared to the control group (significant increase). Dose-dependent elevations were observed both for NF-κB and MAPK8. Accordingly, our assumption was only valid for tartrazin. In particular, in several cases the tartrazine showed a willingness for effect-addition with azorubine exposure in the case of both NF-kB and MAPK8.

Test material for genes that influence the methylation pattern was not found in the available scientific databases, however, the above described results may indicate a known tumor-inducing effect based on our knowledge.

In view of the hypermethylation of cellcycle-regulating genes, allele-loss inactivation and facilitated gene mutation may occur, and that in most of the human tumors the elevated mRNA and protein expression levels of the three DNA methyltransferases described above are typical (Chen and Chan, 2014; Jurasek et al., 2017).

Summarizing our findings in the case of azorubin, we have verified the evidence published so far, since we did not find any signs of tumor-inducing effects. In the case of tartrazin, however, it is significant that both the metabolizing enzymes, the cell cycle control and on the level of genes influencing methylation showed increase, dose-related growth, generation enhancement, interaction with other coloring agents and chemical carcinogens (in multiple cases

effectadditions), which states that tartrazine is a potential risk factor for tumor formation, against a great number of data, which can be found in many places in the literature (TemaNord, 2002; EFSA ANS, 2009a; Australian Government, 2014).

Summary of new findings

1. The single and ten-fold, ADI doses of azorubine do not cause significant gene expression elevations of CYP1A1 and CYP2E1 metabolizing enzymes. The ten-fold, ADR dose of Tartrazin generates significant gene expression increases in CYP1A1 and CYP2E1 metabolising enzymes in a dose-dependent manner, which represents a higher increase caused by a higher dose and its effect on the chemical carcinogen causes a significant increase compared to the levels of the separated dye treated groups' and control group's expression levels.

2. The single and ten-fold, ADI doses of azorubin azorubine do not cause significant gene expression elevations for NF-κB, GADD45α, MAPK8 genes. The single and ten-fold, ADI doses of Tartrazin resulted significant gene expression increases for NF-κB, MAPK8 genes, but for GADD45α no significant difference was observed. The studied food colors show willingness for effect-addition and interaction within the organization.

3. The single and ADI dose of tartrazine produces significant gene expression in the genes affecting the methylation pattern in the case of DNMT1, DNMT3A, DNMT3B, G1-G2 (liver and kidney homogenate - in both sexes), while the ten-fold dose of the substance in both G0-G1-G2 relationships produces a significant increase in gene expression, in a dose-dependent manner (liver and kidney homogenate - in both sexes). In our study, we have been able to detect a dose-dependent increase among generation rates at the expression level (more pronounced in the kidney).

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