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Food Additives and Biotransformation with Cytochrome P450 (CYT P450)

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ABSTRACT

The number of emerging organic and inorganic substances, which are called xenobiotic, is increasing day after day. The potential hazards of these substances are being tested since they are used as drugs and food additives. According to the data obtained from these tests, the harmless ones are released for use. However, it should be noted that these compounds, which are taken as drugs or food additives, are mostly biotransformed with cytochrome P450 in the liver. A large portion of different xenobiotic molecular structures that were biotransformed in the liver can be emptied into the small intestine by a biliary duct and can reenter the organism in their transformed molecular structure. Therefore, it should be accepted that the effects of transformed molecular structures of food additives, especially bread additives, to human must be researched.

Keywords: Cytochrome P450, Xenobiotic, Biotransformation

INTRODUCTION

All foreign chemical substances which enter the body through various means, including pharmaceuticals, other than organic compounds taken in with food are called xenobiotic [1]. Food additives, residues of various pesticides and fungicides, wastes polluting the air and water, exhaust and cigarette smoke are some of the xenobiotic other than pharmaceuticals [2]. A critically important molecule group under the name of bread additives has now been included in these compounds. These molecules are a large part of which are not used as building blocks or intermediate compounds in cells are tried to be water soluble by inactivating through structural modifications with various enzymes in the body cells, mainly in the liver (mucosa and lumen of the gastrointestinal tract, kidneys, lungs, etc.). The chemical modification of xenobiotic with the impact of enzymes is called biotransformation. As xenobiotic are generally tried to be made less effective or ineffective compounds as a result of biotransformation, biotransformation realized for this purpose is also called bioinactivation or detoxication. The purpose is to eliminate the effect of the molecule and dispose of it with urine or feces through the biliary tract.

Biotransformation and Afterwards

However, it is extremely wrong and misleading to think the compounds obtained with biotransformation in various body cells, mainly liver, are completely ineffective and ready to dispose of compounds. Today, it is known that some pharmaceuticals are transformed into more effective (transformation of codeine to morphine [3], and transformation of diphenoxylate to difenoxin [4]) or more toxic compounds (transformation of methyl alcohol to formaldehyde and formic acid [5], transformation of acetaminophen to N-acetyl-p-benzoquinone [6]) as a result of biotransformation. Moreover, it has been observed that an ineffective compound can sometimes be activated as a result of biotransformation in the body (transformation of bacampicillin to ampicillin and transformation of Enalapril to Enalaprilat [7]). It should be noted that this rule also applies to food additives which are foreign substances.

"Food additives" are chemical substances added to foods to improve flavor, texture, color, appearance, and consistency or as preservatives during manufacturing or processing [8]. The term now covers approximately 400 of the 2,600-2,700 substances intentionally added to foods (Code of Federal Regulations, 1981) [9]. About 2.200-2.400 remaining molecules are defined by FDA as GRAS (generally recognized as safe) substances or "unpublished GRAS substances" [10]. Studies on these additives in use today demonstrate that gradually increasing amount of additives is hazardous for health [11,12]. These substances include about 12 additives known to be carcinogenic today [13,14].

It is a fact that the same process is applied to chemical substances which are included in various foods and bread as an emulsifier, flavoring, thickener, preservative, antistaling and coloring agents. Today, it is not clearly known if many additives in food, mainly bread are biotransformed and what are the effects of the substances obtained from these reactions.

Defense in Higher Organisms

Protection from foreign molecules and cells for the healthy functioning of cells in higher organisms is realized mainly by 2 systems. The first is the immune system and leukocytes. This system which collects and identifies information and is destroyer on both cell and molecular levels try to protect the organism from foreign cells and molecules [15].

The second system is the enzymes system which structurally modifies and inactivates foreign molecules. These enzymes which are present in the kidneys, gastrointestinal system, skin and lungs and the most developed of which is present in the liver can be grouped into 2: mitochondrial enzymes and microsomal enzymes. Microsomal enzymes constitute most of the enzymes which take part in detoxication in the liver. Microsomal enzymes which metabolize xenobiotic are also grouped into 2:

- Phase I enzymes: These are the enzymes which change the molecular structure mainly with oxidation-reduction and hydrolysis reactions. This group of microsomal enzymes maintains the most important fraction in the liver which plays the lead role in biotransformation
- Phase II enzymes: These are conjugation enzymes which bind various molecule groups such as sulfate, acetyl and glucuronic acid to structurally modified molecules and make the molecule water-soluble [16]

Cytochrome P450 Enzymes and Activities

Enzymes which realize Phase I reactions are grouped under the name of cytochrome P450 (CYP P450) enzymes. The enzymes are protein molecules which include the "heme" group. There are plenty of cytochrome P450 enzymes in various tissues and organs, mainly the liver, in the human body. Today, 57 different CYP gene areas have been identified in the human body [17]. Synthesized cytochrome P450 enzymes have been divided into 18 groups and 42 subgroups based on the structural similarities in their molecules [CYP2 (CYP2A1/4/5), CYP2B1/2/10, CYP2C6/50, CYP2D6/7, CYP2E1, CYP3 (CYP3A4/11), CYP4A3, CYP8B7A, CYP9, CYP7, CYP17) (F)] [18]. The roles of CYP P450 enzymes can be understood much better when an oxidation reaction in microsomes is examined. As can be seen in the following reaction, the molecular structure is modified as a result of an oxidation reaction catalyzed with CYP P450 enzymes:

$NADPH + H^+ + O_2 + SH \rightarrow NADP^+ + H_2O + S\text{-}OH$

The foreign molecule here is indicated as substrate (S) and binds to the enzyme which is any organic xenobiotic molecule which can have an alkane, alkene or aromatic structure [19]. A part of this foreign substance molecule which entered the organism somehow was oxidated and alienated and made dysfunctional. As only one of two oxygen atoms takes part in the reaction, it is called monooxygenase reaction and the enzymes which catalyze reactions are called cytochrome P450 monooxygenase enzymes [19,20].

Molecules can also be inactivated with a reduction reaction which is the exact opposite of the above reaction again using NADPH in addition to oxidation with Phase I enzymes. Another reaction group catalyzed by Phase I enzymes is the random splitting of molecules. Main reactions in this group catalyzed by CYP P450 enzymes are hydrolysis, decarboxylation, and breaking of the glycoside bonds. Similarly, these reactions are structurally modified and are inactivate foreign molecules [21].

In the next stage, structurally modified molecules are included in conjugation reactions, if necessary, with Phase II enzymes with an aim to make them water soluble and inactivated. Conjugation reactions mean binding a radical or an endogen molecule to a foreign molecule or its metabolite with a covalent bond [22]. Two different conjugation reactions used for various purposes in humans have been identified:

The first group of conjugation reactions constitutes binding a radical or an endogen molecule with a covalent bond to a foreign molecule which enters our body and is structurally modified with Phase I enzymes.

Eight different types of enzymes have been identified to realize the second group of conjugation reactions:

- Binding of the molecule with glucuronic acid through the UDP-glucuronyl transferase enzyme
- Transfer of the methyl group to the nitrogen atom if present in the molecule structure with the N-methyl transferase enzyme (N-methylation)
- Transfer of the methyl group to the oxygen atom present in the molecule structure with the O-methyl transferase enzyme (O-methylation)
- Binding of the acetyl group to the molecule through N-acetyl transferase (NAT) enzymes (N-acetylation)
- Transfer of sulfate groups to the foreign molecule through the sulfotransferase enzyme (sulfidation)
- Binding of the molecule with glutation through the glutation-S-transferase enzyme
- Binding of a different group of enzymes with the molecules with glycine or glutamine
- Other conjugations

Although the purpose of the reactions realized with CYP P450 enzymes is to inactivate the molecule, it should be noted that the organism, starting from the cell where the reaction takes place, faces new molecules or new forms of the molecule. For example, sorbic acid (E200) is an antibacterial and antifungal additive use to preserve food. It should be acknowledged considering the available data that it is taken into the body by absorption through the digestive tract based on the fact that it may cause a rash and allergic reactions when taken with food. Sorbic acid, as in all xenobiotic, will be directly discharged through urine or transferred to the liver. If sorbic acid is transferred to the liver, it will be inactivated with CYP P450 enzymes. To this end, sorbic acid can be transformed into sorbic aldehyde (sorbaldehyde) or sorbil alcohol (sorbalcohol) with one of only two reactions. It is also possible to add methyl or sulfate groups to the molecule. From the available research, it can be seen that both sorbaldehyde and sorbalcohol molecules produced with Phase I reactions are toxic substances. Similar reactions are also applicable for another antibacterial and antifungal substance, benzoic acid [23].

CONCLUSION

The purpose of this paper is to draw attention to the possibility that these additives which are taken in through various means and can be present in the liver with their new forms in addition to their already tested forms can be harmful to the organism with their new forms. As known, all waste materials inactivated in the liver and bilirubin are sent to the gall bladder with bile acids and are discharged to the intestines with the contraction of the gall bladder with the impact of the cholecystokinin hormone during digestion. What is expected here is the disposal of xenobiotic residues with feces. However, all chemicals discharged to the intestinal lumen are reabsorbed. It can be seen clearly tracking down the route followed by bilirubin which is generated by splitting of the erythrocytes. As known, the indirect bilirubin generated in RES is carried to the liver with albumin and after binding with glucuronic acid through CYP P450 Phase II enzymes and becoming water soluble; it is transferred to the gall bladder for disposal. First, glucuronic acid splits from the structure of the direct bilirubin left to the digestive tract with gall in the intestinal lumen and then it oxidizes and transforms into urobilinogen and stercobilin. It is observed that the urobilinogen produced here is partly reabsorbed and mixed with blood. Urobilinogen is the substance which gives urine its yellow color and it is taken from the blood in the kidneys and disposes of in urine.

It is necessary to accept this process as it is applicable for all waste materials fed to the digestive tract with gall. Therefore, it is required to study and carefully observe the results of not only the additives added to various foods and bread but also the metabolites which can possibly be generated before offering them to the use of consumers.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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