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Review

Gut Microbiota: Formation, Lifelong Development and Relation to Cytochrome P450 System, Diseases, Drug Bioavailability and Drug Interactions

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ABSTRACT

The human microbiota is an essential and individual part of the human body composed of microorganisms that live in symbiosis with the human body. It is formed prenatally and changes throughout a person's life due to endogenous and exogenous factors such as birth, geography, gender, sex hormones, genetics, mode of birth, age, lifestyle, nutrition, use of antibiotics, and disease-related changes. Studies on the microbiota have mostly focused on its relation to diseases, but the gut microbiota is also very sensitive to xenobiotics, which directy or indirectly alter the pharmacokinetics of drugs used by the host. Although the gut microbiota recovers in a few weeks, some changes may be permanent. It is important to consider changes in drug bioavailability in patients who were recently or currently treated with antibiotics for the safe and efficient pharmacotherapy of patients. With advanced knowledge about the microbiota and advances in the field of microbiome genetics, it may be possible that in the future, a person's microbiota map is used in personalizing drug treatment. In this review, we aim to emphasize the importance of microbiota and drug interactions.

Keywords: Microbiota, bioavailability, pharmacokinetics, personalized medicine, CYP P450s

INTRODUCTION

The human body is composed of trillions of cells. While 10% of these are human cells, 90% are microbial cells located in this macroscopic host (1). All microorganisms found in humans are called "microbiota" and the genome of microorganisms is called "microbiome" (2). The term microbiota is very old; however, the knowledge of its importance and relationship to diseases dates back only to a decade or two. The skin, mouth, vagina, gastrointestinal, urinary system, or even the placenta contain various microorganisms (3) and therefore form the different types of microbiota like the gut microbiota, oral microbiota, skin microbiota, vaginal microbiota, and urinary microbiota.

The microbiota mediates several functions including the production of essential vitamins, toxin detoxification, regulation of cholesterol metabolism, bile deconjugation, inhibition of pathogenic microorganism colonization, and regulation of gene expression of microbial metabolites such as short-chain fatty acids production for epithelial cells. Therefore, the microbiota is a basic part of a healthy life (4).

The human microbiota has a multifactorial interaction and changes throughout a person's life due to endogenous and exogenous factors like geography, genetics, mode of birth, age, lifestyle, nutrition, use of antibiotics and disease-related changes (5).

Mode of delivery and maternal microbiome transmitted by birth, nutrition during infancy, diet, habitat, social interaction, exposure to xenobiotics, pathogen, and parasitic organisms have been shown to be environmental factors affecting the formation of the microbiome content (6). Microbiota begins to form in the human body during the intrauterine life. The first stage of a baby's microbiota forms when the newborn comes into contact with microorganisms in the vaginal canal of the mother. With normal birth, the maternal microbiota passes predominantly to the child. In general, permanent microbiota develops at the end of the first month after birth (7, 8). Considering all these, it is thought that each person has an unique microbiota. The Human Genome Project (Human Genome Project-1990–2003) and the Human Microbiome Project (Human Microbiome Project-2008–2012) are two important projects that have as a common goal to analyze the characterization of the human microbiota and its role in human health and disease (9). Another important project on this topic is the ELDERMET Project, which was conducted between 2007–2013, in which the relationship between the diet, microbiota, and functional outcomes was investigated and associated with diseases in 500

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elderly Irish persons >65 years. It was outlined that changing the gut microbiota by altering the diet may promote healthy aging, which is associated with microbial diversity (10, 11). Although there are many studies examining the state of the human microbiome in disease and health status, these projects mostly focused on the relationship between microbiome and diseases (12).

Our microbiota contains a certain proportion of beneficial bacteria and opportunistic pathogens (13). When this ratio of beneficial/opportunistic pathogens decreases, a pathological process called "microbial dysbiosis" begins. This has been found to be associated with many diseases including cancer, non-alcoholic fatty liver disease, obesity, diabetes, coronary heart disease, kidney dysfunction, and neurodegenerative disorders (2-4, 7, 14, 15). When using drugs, this important factor should also be taken into consideration as conditions such as drug side effects, decreased drug efficacy, or drug toxicity may be related to the patient's microbiota (6, 7, 15). This review summarizes the formation and development of gut microbiota and the relationship between gut microbiota and diseases, drug bioavailability, and the cytochrome P450 (CYP) System.

Formation and Development of Gut Microbiota

Formation of the microbiota in the human body starts in the prenatal period. It is mainly shaped in the first three years of life, and feeding style plays an important role in the development of a healthy microbiota (16, 17). Infancy microbiota contributes to the development and maturation of the gastrointestinal mucosa. Breast milk is thought to contain especially Bifido bacteria. The gut microbiota starts to take shape during birth. After birth, it changes with factors such as the use of antibiotics, diseases, infections, hormonal changes, circadian rhythm, and nutrition. Subsequently, certain changes occur in the microbiota with aging (18). Studies have examined the importance of being exposed to microorganisms and microbiota development has been found to be an important determinant of the child's future health status (17). In humans, the digestive system microbiota begins to take shape immediately after birth. During delivery, the newborn encounters many microorganisms in the vaginal canal of the mother leading to the formation of the microbiota of the digestive tract. Studies in newborns have shown that the mode of delivery is directly related to the baby's digestive system microbiota. In babies born through vaginal delivery, their gut microbiota is composed of microorganisms of the mothers' genitourinary system, while for those born by cesarean section, their gut microbiota is similar to that of the maternal skin microbiota (8, 19). Other important factors affecting the gut microbiota of infants include the diet, gestational age, hospitalization, and frequent antibiotic use during the infantile period (17-20). Studies in geriatric populations have shown that there is significant reduction both in bacterial density and diversity of the microbiota with aging (17, 21).

Main Points:

- The development of gut microbiota which is essential for a healthy life, starts to take shape during birth in the vaginal canal and changes throughout life due to many factors.
- Gut microbiota is metabolically active and contains their own CYP enzyme systems which can alter the pharmacokinetics and thus the therapeutic results of an administered drug.
- The ratio of beneficial/opportunistic pathogens in the gut is important and changes in gut microbiota composition is associated with many diseases including cancer, non-alcoholic fatty liver disease, obesity, diabetes, coronary heart disease, severe asthma, food allergies, autism, major depressive disorders, kidney dysfunction and neurodegenerative disorders.
- The effects of antibiotics on microbiota composition, metabolism and host interaction are dramatic and may change the efficacy of a drug drastically.
- Knowledge of interaction of microbiota and drugs is essential for safe and efficient pharmacotherapy of patients and individual differences in gut microbiota are an important obstacle in choosing drug treatment.

Relationship Between Gut Microbiota and Diseases

There is increasing evidence that gut microbiota is associated with many diseases (5, 15, 21, 22). Infection is one of the most common diseases that occur as a result of microbiota dysbiosis. Most importantly, infectious diseases and their treatment have a great impact on the human microbiota, which determines the outcome of infectious diseases in the human host. Pathogenic microorganisms colonize the intestinal mucosa, thereby resulting in the induction of a strong inflammatory response, followed by translocation of the intestinal bacteria. Chronic inflammation associated with *Helicobacter pylori* is thought to be the strongest risk factor for gastric cancer (23-26).

An increasing number of *in vivo* and human studies have shown that the interaction between the gut microbiota and host genotype or dietary changes may be important contributing factors to obesity and related metabolic disorders (3, 7, 25, 26). Studies have shown that the gut microbiota is an important modulator. It is an established fact that the gut microbiome changes according to dietary intake (4, 6). Gut microbiome is regulated by circadian rhythms via intrinsic circadian clocks as well as via the host organism. Furthermore, recent studies have shown that the gut microbiota affects the circadian rhythm and is itself exposed to circadian oscillations (27, 28). It has been shown that bacterial rhythms in female mice are more robust than those observed in male mice (29). Gut microbiota differs according to sex (30) *Lactobacillaceae* are more prevalent in women, while *Ruminococcaceae* and *Rikenellaceae* are more common in men. Furthermore, *Bacteroides* and *Prevotella* bacteria were found to be more prevalent in males than in females in females in a cohort (31). Testosterone, which is responsible for the microbial difference between the sexes has an impact on the gut microbiome. The gut microbiome is affected and regulated by estrogen and testosterone levels (32, 33). Testesterone and non-ovarian estrogen levels can also be affected by alterations in the gut microbiome. In a cohort investigating the contribution of microbiome to extra-ovarian estrogen levels, a correlation was found between men and postmenopausal women and estrogen levels.

There is increasing evidence that changes in the microbiota are involved in the pathogenesis of other diseases such as severe asthma, food allergies, autism, and major depressive disorders (15, 34-36). Human studies of the gut microbiota in food-allergic individuals have yielded variable findings because food allergy is a complex and heterogeneous disease. More studies are needed on gut microbiota and food allergies (36). There is evidence that allergic asthma susceptibility increases with antibiotic-induced changes in the gut microbiota (35, 37).

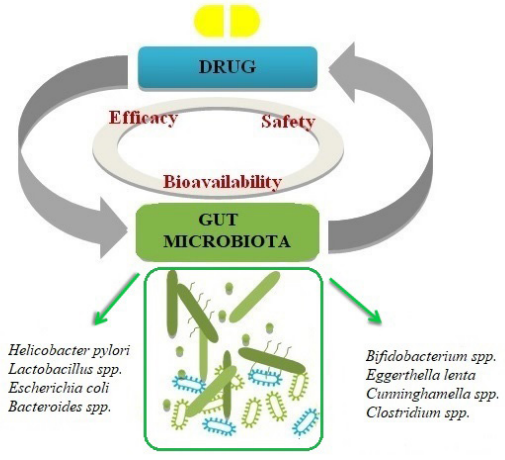
Microbiota differs between genders, both in animal models and in humans. Immunity is affected by sex hormones. The "microgenderome" is the term used for the sexually dimorphic microbiome and defines the interaction between microbiota, sex hormones, and the immune system. Sex differences in systemic immunity and susceptibility to a multitude of infections and chronic diseases are influenced by the gut microbiota. The gut microbiota drives multiple interactions locally with immune cells that regulate the homeostatic environment. The course and treatment of diseases in males and females including psychological disorders such as anxiety and depression and psychosomatic disorders such as irritable bowel disease are affected differently due to the microgenderome. Treatment of these disorders by changing the microbiota with pre-, pro-, syn- and post-biotics, is sometimes a therapeutic option that will respond differently in males and females (38-41).

Relationship Between Gut Microbiota and Drug Bioavailability

Many studies have suggested that the gut microbiota has metabolic potentials equivalent to that of the liver. It is also known that gut microbiota influences drug pharmacokinetics by the direct metabolism of xenobiotics or the indirect interaction with the host enzyme system. Human and animal studies have shown that the gut microbiota has a variety of metabolic activities and can alter the pharmacokinetics and thus the therapeutic results of an administered drug. Studies have suggested that the suitability of the microbiota should be considered when determining the pharmacokinetics of a drug (42).

In addition, a newly developed drug may have more microbial interactions if it has a low solubility or permeability and a long passage time in the gastrointestinal tract, leading to a marked change in the effect of the drug. An example for this is amiodarone, a class III antiarrhythmic drug, which shows marked increase in its bioavailability due to the increased formation of active metabolites, when exposed to the *Escherichia coli* strain *Nissle 1917 (EcN)* in the gut (43). *Helicobacter pylori (Hp)* reduces the absorption of levodopa, a drug commonly prescribed in Parkinson's disease (44). It has been shown that the efficacy of simvastatin, a prodrug used in the treatment of primary hypercholesterolemia, varies in the presence of *Lactobacillus bacteria* (45). Changes in the bioavailability of nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, indomethacin, or ketoprofen have been related to an increase in microorganisms containing β-glucuronidase like *Bacteroides, Clostridium, and Bifidobacterium spp* (46). Irinotecan, an antineoplastic drug for the intravenous treatment of colorectal cancer, may lead to drug toxicity due to an increase of the active metabolite of the drug, SN-38 (7-ethyl-10-hydroxycamptothecin), when the microbiota contains excess amounts of *Escherichia coli, Bacteroides vulgatus, Clostridium ramosum,* or β-glucuronidase (47). *Eggerthella lenta* can reduce drug bioavailability by causing the inactivation of digoxin and hence may cause problems in patients taking the drug (Figure 1) (48).

Figure 1. The human body contains many different microorganisms. Depending on the type and amount of these microorganisms, the efficacy, safety and bioavability of drugs which are taken changes. Gut microbiota may effect the bioavailability of drugs by microbial enzyme activity, drug pharmacokinetics by the direct metabolism of xenobiotics or interaction with host enzyme systems



When talking about bioavailability, the relationship between antibiotics, a widely used drug group, and the microbiota should not be ignored. The effects of antibiotics on microbiota composition, metabolism, and host interaction are dramatic. It may take several weeks for the altered microbiota to recover after antibiotic treatment. However, there are also studies indicating that the population of some subtypes of bacteria in the microbiota can be affected permanently. Therefore, when using antibiotics, it should be taken into consideration that the bioavailability of other drugs used by the patient may be affected.

Relationship Between Gut Microbiota and the Cytochrome P450 System

Cytochrome P450s (CYPs) are a group of enzymes metabolizing xenobiotics. The activity of CYP P450 is altered by various factors such as gender, the environment, disease, alcohol, and drugs. Diet is another important influential factor. Cytochromes involve individual, interindividual, and interracial genetic polymorphisms. The metabolic activity of the microbiota is related to CYP enzymes catalyzing phase I and II reactions in drug metabolism (49, 50).

There are a lot of CYP isoforms in humans. It is known that CYP enzymes are involved in drug metabolism in humans. Cytochromes are found in many different tissues of the human body including the intestine and liver. The majority of drug oxidation appears to be related to the main enzymes: CYP 2D6, 2C9, 1A2, 2C19, 2E1, and 3A4. The most important CYP enzymes are CYP3A4 and CYP2D6. CYP3A4 is expressed in both liver and intestinal tissue. It is

also involved in extrahepatic metabolism. The human intestinal tissue has the ability to metabolize drugs. CYP enzymes are associated with a majority of phase I drug metabolism reactions (50, 51). There is an association between CYP cytochrome and different diseases and nutritional and environmental toxic effects. Cytochromes demonstrate interindividual genetic variation. Gut microbiota regulates liver and metabolic functions, regulates the secretion of bile acids, and participates in the pathogenesis of alcoholic and non-alcoholic fatty liver disease (14). Cytochrome P450 enzymes oxidize substances and are also able to metabolize. CYP enzymes are involved in reactions including O-dealkylation, S-oxidation, epoxidation, and hydroxylation. The activity of cytochrome P450 is influenced by a variety of parameters, such as genus, environment, diseases, alcohol use, smoking, diet, and drugs. Diet plays an essential role and has effects on the metabolism of xenobiotics. Cytochromes have different interindividual polymorphisms (49, 51). The gut microbiota possesses a metabolic capacity because of phase I (oxidative) and phase II (conjugative) drug metabolism. Bacteria have been shown to express CYP genes. Human cytochrome P450s play important roles in the bioactivation and detoxification of numerous therapeutic drugs. The first-pass metabolism of orally administered drugs is related to drug-metabolizing enzymes, P450s, and the gut microbiota. Genetic polymorphisms in P450 genes may affect the pharmacokinetics of their drugs (52). The molecular mechanisms of the interaction between gut bacteria and the metabolism of drugs by the host warrant further research. *Cunninghamella spp. elegans, C. Blakesleeana,* and *C. echinulata* have been employed in the transformation of drugs and xenobiotics via phase I and phase II reactions. The transformation of drugs and xenobiotics in *Cunninghamella spp* involves a number of reactions catalyzed by different CYP isoforms. For example, flurbiprofen is transformed to 40-hydroxyflurbiprofen by *C. elegans* and in humans, this transformation is catalyzed exclusively by CYP2C9 (50). Phase II metabolism of drugs by *Cunninghamella spp.* has been reported to be less frequent. *Bacillus megaterium* is found in the human ileum and can express CYP102, which can affect the cell cycle in epithelial cells. CYP102 in *B. megaterium* can be induced by barbiturates like phenobarbital indirectly, peroxisome proliferators, and nonsteroidal anti-inflammatory drugs. Taken regularly, ibuprofen and other drugs create an environment that is favorable to the pathogens in the gut microbiome (53).

In addition to bacterial P450s, fungal P450s present a new area for xenobiotic biotransformation. Fungal P450s can metabolize antibiotics, β-blockers, and anti-inflammatory drugs (54). The function of microbiome P450s is affected by drugs. It is important to understand how microbial P450s may influence host health and drug efficacy.

Regulating microbial P450s may be important for personalized medicine and drug bioavailability. Due to the fact that irinotekan is changed to its active metabolyte by β-glucuronidase, the inhibition of β-glucuronidases by *Escherichia coli* prevents the toxicity of the drug. Thus, inhibiting or inducing microbial P450s may be a new method of altering the pharmacokinetics of drugs (46, 47, 50, 53).

When the urinary metabolite ratio of acetaminophen metabolism was investigated with regard to the microbiome, patients who had high urinary levels of p-cresol sulfate before exposure to acetaminophen had a low acetaminophen to acetaminophen glucuronide ratio. In another study, probiotic exposure of *Lactobacillus reuteri* KCTC3679 increased the metabolism of acetaminophen, decreased the AUC (Area Under the Curve) of oral acetaminophen, and increased the bacterial load of *L. reuteri* as well as that of cyanobacteria (55).

Cytochromes show interindividual and interethnic genetic polymorphisms. Changes in the pharmacokinetic profile of drugs are associated with toxicity, reduced metabolism, and adverse drug interaction. The high metabolic capacity of the gut microbiota is due to enzymes, which catalyze reactions in phase I and phase II drug metabolism. However, drug discovery studies lack focus on the gut microbiota. Understanding the importance of gut microbiota may be essential to providing personalized medical healthcare. In the future, human gut microbiota may play an important role in the metabolism and oral bioavailability of drugs.

CONCLUSION

The importance of the human microbiota in health and disease is receiving increasing attention. The gut microbiota is essential for a healthy life. Knowledge of the interaction between the microbiota and drugs is essential for the safe and efficient pharmacotherapy of patients. Individual differences in the gut microbiota are an important obstacle in choosing a drug treatment. With advanced knowledge about microbiota and advances in the field of microbiome genetics, it may be possible that in the future, a persons microbiota map is used in personalizing drug treatment. Gut microbiota-drug interaction is explained by the changing toxicity, metabolism, absorption and efficacy parameters of the drug and gut homeostasis. Gut microbiota is another metabolically active compartment together with the classical drug metabolism in the body, including the liver that affects the bioavailability, safety and efficacy of drugs. In addition, the gut microbiota may be a good target for regulating drug pharmacological or toxicological effects. Since the gut microbiota plays a major role, these factors should be investigated in the future.

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