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The Gut Microbiome and Pre-systemic Metabolism: Current State and Evolving Research

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Abstract

The evolution of the complex metabolic interaction between intestinal microbiota in the human gut with its host is multidimensional. Our understanding of this complex interaction has evolved in the past years either with the use of more sophisticated analytical techniques or by reported adverse drug effects that have been associated with intestinal drug metabolism such as with sorivudine. The composition of the intestinal microbiome is initially determined by environmental and genetic factors although external influences as well as host immune reactions provide for adjustment of the delicate balance in both health and disease conditions. The metabolism of drugs by both intestinal bacteria and further by enterocytes leading to their systemic absorption deserves further attention and may provide valuable insights into pre-systemic drug metabolism, delivery, and toxicity. A better understanding of the metabolic pathways may aid in the drug development and toxicity evaluation process.

Keywords: microbiome; toxicity; pre-systemic drug metabolism; symbiosis

Abbreviations: TLRs: Toll-Like Receptors; MAMPs: Microbial Associated Molecular Patterns, 5-FU: 5-Fluorouracil; P-gp: P-glycoprotein; UGT- UDP-glucosyltransferase

Introduction

The evolution of our understanding of the processes involved in drug metabolism has considerably influenced the field of drug discovery and toxicity over the past three decades. While simple models initially only considered the liver as the main metabolizing organ in the body, over time and with the introduction of new drugs came the realization that any substance entering the human body is subjected to a number of different metabolic modifications. There are several factors that influence drug metabolism including route of administration, dose, genetics, disease state, and metabolic activity [1]. Certain structural features of xenobiotics are known for being metabolized via a certain pathway depending on the route of administration and some functional groups have been added to modify the physiochemical properties, increase the absorption, or target specific organs for the active drug to reach via synthesis of an inactive pro-drug [2]. Dose-dependent absorption and metabolism occur through transporters and enzyme saturation that may then lead to adverse effects and toxicity as well as increased or decreased serum concentrations of the active drug [3]. Genetic differences such as enzyme polymorphisms, disease states, and metabolic activity differ widely among individuals [4]. All of these variables are well known to contribute to drug metabolism and effect and have been considered for decades even for models that only involve the liver and the blood-soluble enzymes as places of metabolic activity. However, as early as the 1970s, investigations into the metabolic capacity of the intestinal bacteria and the enterocytes have revealed a specific and diverse contribution to the metabolism of a wide array of xenobiotics [5].

With the emergence of more sensitive and specific analytical techniques as well as the establishment of new interdisciplinary sciences such as systems biology, molecular medicine, next-generation sequencing technology, bioinformatics, and various metagenomics and metabolomics approaches it is now possible to evaluate much more complex biological systems such as the microbiome in the human gut. The total number of bacteria that colonize the human gut are in the order of 100 trillion and represent one of the most complex biological microecosystems on the planet [1,6]. In addition, the symbiotic nature of the interaction between gut bacteria and the host appears to be specifically tuned for the metabolic and immune functions that the host requires [7].

This review seeks to provide an overview of the complex interactions between the gut microbiome and the host concerning drug metabolism and the development of toxicity as well as various disease states.

The intestinal microbiome and the brain-gut axis

It is well known that the intestinal microbiota develops shortly after birth while the intestines are completely sterile *in utero* [8]. The colonization with bacteria can be predicted to some extent by the culture and environment an individual is living in [9,10]. Such factors as diet, genotype, and microbial interactions contribute to the diversity but also the relative homogeneity of the intestinal microbiome. The two bacterial phyla Firmicutes and Bacteroidetes predominate the bacterial population of the intestines [10,11] although a more thorough investigation reveals a much more diverse bacterial population that results in hundreds of species and thousands of strains thereby constituting a unique fingerprint for each individual [12]. The discovery of this diversity has been made possible by using advanced analytical techniques such as 16S rRNA-targeted oligonucleotide fluorescent probes [13,14] or mass spectrometry and nuclear magnetic resonance techniques [15]. The combination of these techniques allows for the differentiation among the microbiome composition as well as the metabolic phenotype of

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each individual [16]. The development of a stable microbiome is mainly influenced by competitiveness and alterations in the local environment (e.g. pH, retention time, oxygen availability) that allows for optimal growth of certain bacterial strains while inhibiting or reducing the spread of other species and strains [17]. In addition to the competition-centered view, the niche establishment and adaptability of the microbial spectrum accounts for the inter-individual variability depending on a number of factors that allows a readjustment of the equilibrium of bacterial strains and species [18].

One factor to consider in microbial composition is diet. In newborns, the microbiome is mainly composed of strains inherited from the mother and the environment as well as what is transmitted with breast milk. This changes significantly when switching to formula and later to solid food [17,19] especially when the diet is being switched in its chemical composition. This is mainly based on the ability of intestinal bacterial strains to metabolize a wide range of substrates that are chemically similar with the exception of a few specialized strains that are mainly metabolizing sulfur-containing compounds or fibers and inulin (phyla of proteobacteria, bifidobacteria, and firmicutes) [20,21]. Furthermore, the balance between microbial species as well as with the host is mainly symbiotic since certain strains utilize the metabolic products from other species as secondary fermenters in addition to host-derived resources that provide a diverse microbiome [22].

Dynamic microbiome-host interactions

The realization that the intestinal microbiome interacts with the host has been recognized for several different areas. Examples include symbiotic interaction for optimal food processing and local environment variables for optimal growth conditions of prevailing species, immune interactions that benefit the host and maintain a healthy mucosal barrier between intestinal bacteria and the host and the brain-gut axis which is influenced by both the microbiome and the host [8,15]. The symbiotic interaction between host and microbiome for food processing and digestion has been shown for bile acid metabolism and enterohepatic recycling [15] as well as for metabolism of a variety of drugs and nutritional supplements [1,23,24]. Such symbiotic interactions develop shortly after birth and remain fairly constant in the healthy population whereas acute disease states or loss of bacterial equilibrium following antibiotic therapy may account for the development of chronic disorders that can permanently affect the ability of the host to process food optimally [25,26]. It appears that both the host genotype and the metabolic phenotype are at least in part influenced by the composition of the intestinal microbiome and the host genotype also influences the colonization of the intestines by microbes [7,16,23]. Both gender and ethnicity play a role in microbiome composition and metabolic activity as has been shown when comparing intestinal microbial composition in a Chinese family study with that of American and European families [16,27,28]. Certain bacterial strains play a vital role in metabolism of nutrients such as choline or taurine; both of which are essential to the absorption of fatty acids by the host [15,29]. The evolutionary establishment of a symbiotic microbiome-host interaction has been exemplified by metagenomic sequencing that shows an adaptive process to allow bacteria adherence to the gut wall and splitting of metabolic activities. While gut bacteria mainly utilize sugars for energy production leading to generation of short-chain fatty acids such as acetate, propionate, and butyrate, the host utilizes these metabolic products for its energy consumption – muscles, heart, and brain utilize acetate while butyrate is important for enterocytes [30]. Furthermore, bacteria in the gut provide the host with essential amino acids and generate vitamins A and K as well as biotin [31]. Although the host genotype contributes to the diversity and specific composition of some bacterial species, environmental factors such as diet and initial colonization after birth show a stronger influence [32].

Immune-linked microbiome-host interactions

From birth on the intestinal mucosa is faced with a huge diversity of bacteria that colonize throughout the gastrointestinal tract. Because the surface area of the intestinal tract is the largest connected surface in the human body, the antigenic microbial challenges that the body faces are extensive and require a delicate balance between maintaining commensal bacteria that benefit the host and building an effective defense system against invading bacterial species [33]. Pattern recognition receptors (PRRs) such as toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs) and microbial-associated molecular patterns (MAMPs) which include lipopolysaccharides, peptidoglycans, or formylated peptides, as well as immune cells regulate the growth of microbiota and are able to distinguish between symbiont and pathogen [33,34]. The regulatory pathways mediated through PRRs include nuclear factor κB (NFκB), mitogen-activated protein kinase (MAPKs) and caspase-dependent signaling cascades [33]. Commensal bacteria limit the pro-inflammatory response of the host to invading pathogens through regulation of the NFκB and caspase-dependent pathways. This may then lead to either induction of apoptosis of the invading pathogen or limitation of the inflammatory response to the surrounding area of the pathogen. Both the innate and the adaptive branches of the host immune system contribute to the complex balance of the mircobiome-host interaction. The host can release reactive oxygen species to fight off pathogens but at the cost of temporary loss of symbiotic bacteria as well. The innate immune system develops early after colonization with commensal bacteria by adapting to the presence of symbiotic bacteria through expression of intra-epithelial lymphocytes. Especially the expression of fucose as the terminal moiety on epithelial glycans allows for colonization of commensal bacteria because these bacteria utilize fucose as an energy source [35]. TLRs play a vital role to monitor the microbiome and limit access to the lumen while causing an immune response if microbes are detected on the basolateral side of enterocytes or directly in the subepithelial layer [36]. Furthermore, commensal bacteria can directly regulate the expression of TLRs through activation of immunosensory MAMPs. MAMPs are also utilized by commensal bacteria and the host innate immune system to activate pro-inflammatory mediators and promote T-helper cell responses [37]. The adaptive branch of the immune system is divided into four subtype T helper cells which have specific functions by secreting a vast array of pro- and anti-inflammatory mediators such as interleukins, interferons, and immunoglobulins [33,38]. In addition to maintenance of the microbiome equilibrium, the intestinal mucosa can contribute to or facilitate the development of inflammatory disorders when the signaling cascade involves increased levels of pro-inflammatory signaling molecules (interleukins and neutrophils) and stress-mediators (norepinephrine and corticosterone) [12,38,39]. This leads to a chronic suppression of commensal microbes in the gastrointestinal tract which in turn causes mucosal damage that triggers an inflammatory and immune response [40].

The enteric nervous system or brain-gut axis

The complexity of the interaction between the microbiota in the gut and the host is bidirectional and appears to be influenced by the brain-gut axis [7]. These interactions are through neuronal, endocrine, and immunologic mechanisms that influence both the host as well as

the microbiome [40,41]. The bacteria closest to the gut wall appear to be more affected and interact with the host compared to the more lumen-centered bacteria. This has been linked to the mucin layer that prevents diffusion of most bacteria but allows for certain commensal bacterial strains to remain closer to the gut wall [33]. The differential distribution of bacteria in a cross-sectional segment of the intestines shows a relationship with the degree of interaction with the host as has been evaluated in healthy controls compared to patients suffering from a variety of chronic gastrointestinal inflammatory disorders [34,42,43]. Controlling the delicate balance between the microbiome activity and metabolic processes, the brain-gut axis has a number of ways to indirectly or directly interact with the microbiota. Furthermore, the host can directly influence the activity of the mircobiome through secretion of neurotransmitters and biogenic peptides such as serotonin, acetylcholine, corticotropin-releasing factor, norepinephrine, or dynorphin [40]. Both serotonin and acetylcholine are the main neurotransmitters that mediate intestinal motility and also function as a feedback mechanism to signal any discrepancies [44]. The release of these endogenous factors also influences pain perception, motility, and residual time of microbes in the intestinal lumen. Infections may cause a dysfunction or inhibition of the excretion of serotonin via inhibition of serotonin transporters [45] which then may lead to decreased motility and hypersensitivity.

The implications of the microbiome composition and how it interacts with the host play a significant role both in the healthy population but even more so in disease states that require therapeutic intervention. Changes in the pre-systemic metabolic profile of either the microbiome or the host can contribute to variability in metabolite concentrations among patients in addition to the usual variation attributed to hepatic enzyme polymorphisms. A better understanding of the interplay between microbial and enterocyte metabolism is important for drug design, development, and clinical outcome of drug treatment.

Complexity of microbiome and enterocyte metabolism of drugs

In recent years, presystemic metabolic activity has been recognized as a significant contributor of drug metabolism [46,47]. This has been emphasized through various reports that linked toxicity and even fatalities to combined microbiome and enterocyte metabolism.

Enterocyte metabolism

Enterocytes are the most common cells lining the intestinal tract and are known to express CYP 450 enzymes, especially CYP 3A4 and CYP 2C family members as well as phase II metabolizing enzymes such as UDP-glucosyltransferase (UGT) and sulfotransferase [48]. Despite the metabolic activity of the CYP enzymes in the small intestines, its contribution to the systemic metabolism of drugs appears to be low or even negligible in comparison to the liver [49]. However, phase II conjugation enzymes and especially sulfotransferase activities are approximately 250-300% higher in the jejunum compared to the liver [48]. The absorption and gut wall metabolism of drugs is different from the mechanics involved in hepatic metabolism since protein binding does not occur and many drugs first have to enter the enterocytes before being subjected to metabolism, mainly CYP 3A4 substrates which may present with a significant intestinal first-pass metabolism [50]. Another factor contributing to drug metabolism in enterocytes is the permeability of the drug compound. While lipophilic compounds are readily absorbed in the gut and are then subjected to metabolism, hydrophilic substances may require active transporter systems that limit their absorption. Further reduction in systemic absorption is then a result of gut wall metabolism with the potential of excretion of the metabolite back into the intestinal lumen [48]. The multi-drug resistance protein (MDR) family is highly expressed on the apical side of enterocytes and serve as a mechanism of reduce systemic absorption of a compound and its metabolites by excreting absorbed molecules back into the lumen [51]. The most abundantly present MDR transporter is P-glycoprotein (P-gp) of which many drugs are substrates [52]. This transporter protein works to excrete already absorbed compounds out of the cell thereby reducing their systemic bioavailability. Several drugs have been shown to be substrates while other drugs are inhibitors or inducers of P-gp [53]. This further complicates the potential for drug interactions and toxicity especially if a substrate for P-gp is given together with an inhibitor.

Microbiome metabolism

The diversity and amount of bacteria is specific to the parts of the intestines with the highest amount of bacteria being present in the descending colon at approximately 10^{12} bacteria/g wet weight [1]. Despite the diversity of bacterial strains as mentioned earlier in this review article, the metabolic processes are mainly centered around reduction and hydrolysis reactions with only a minor fraction accounting for cleavage, degradation, and coupling reactions. Reduction is the most common type of metabolic bacterial reaction since most species on the gastrointestinal tract are facultative anaerobic bacteria (such as *Escherichia and streptococci*) or entirely anaerobic species [54]. Although the number of bacteria is lower and the transit time is shorter in the smaller intestines because of the lower pH associated with the digestive fluids entering from the stomach, the exposure area and higher absorption of drugs into the body from this section of the gastrointestinal tract make it the most important contributor to microbiome metabolic activity [55]. One common reduction reaction is azo-reduction of azo-containing compounds to mostly inactive primary amines. This has been studied for prontosil and sulfasalazine as well as their structural derivatives [56,57]. In addition, nitro-groups are common targets for bacterial reduction reactions which also result in mostly inactive primary amine metabolites as has been observed for nitrazepam, clonazepam, and misonidazole [58-60]. In some cases, this metabolic conversion actually leads to the generation of the active metabolite that is then readily absorbed for systemic effects or acts locally in the intestines. Reduction of sulfur compounds is also common in microbiome metabolism. Examples of sulfur-containing compounds that have been shown to be reduced to sulfite metabolites are omeprazole, sulindac, and sulfinpyrazone although some of these studies were conducted in animals and not humans which may indicate differences in metabolic profile [1]. These metabolites are still being absorbed and the extent of the same metabolic reaction happening in the liver is unknown. Hydrolysis is also a very common metabolic reaction catalyzed by microbes in the intestine. Sorivudine, mentioned above, is an example of hydrolysis that is associated with significant toxicity. Another example is lactulose, which is commonly used to soften stool consistency. Its activation seems to be dependent on hydrolysis by bacteria in the intestines to lactic and acetic acid which stimulate water secretion into the lumen by lowering the pH of the intestinal environment [61]. Other reactions that are catalyzed specifically by gut bacteria include the removal of succinate groups [1], dehydroxylation [62], proteolysis [63], deconjugation and formation of glucuronides and sulfates [64-66], as well as N-demethylation [67].

A specific microbiome-enterocyte interaction is linked to the death

of 18 patients following the combined administration of the antiviral drug sorivudine together with 5-fluorouracil [68]. 5-Fluorouracil (5-FU) is a common chemotherapeutic and is exclusively metabolized in the liver by dihydropyrimidine dehydrogenase (DPD) to a less toxic metabolite, dihydro-5-fluorouracil which is further degraded to α-fluoro-β-alanine. The enzyme DPD therefore is an important regulator of the plasma levels of 5-FU since almost 85% of a given i.v. dose of the chemotherapeutic are inactivated via this route. Oral pro-drugs of 5-FU such as tegafur can be given which are metabolized via CYP 450 enzymes in the enterocytes and liver to the active drug. The antiviral drug sorivudine was introduced in 1993 for the treatment of herpes zoster infections and was approved for combination use with 5-FU pro-drugs. Sorivudine is metabolized exclusively by the gut microbiome to (E)-5-(2-bromovinyl)uracil (BVU) which is then further metabolized by DPD to dihydro-BVU after absorption. BVU itself causes suicide inhibition of DPD during this metabolism step. With DPD being inactivated, plasma levels of 5-FU were reaching toxic levels causing myelo-toxicity and severe intestinal toxicity. The combined use of both drugs had not been evaluated in preclinical or clinical studies before it was approved leading to the death of at least 18 patients after approval and 15 patients during phase II clinical trials. Sorivudine has been taken off the market days after the incident was reported. This is a sad example that illustrates the complexity of potential interactions between microbiome and enterocyte metabolism and how it can affect the toxicity of drugs.

Despite such significant interactions, the interrelationship between the microbiome and enterocyte metabolism has been demonstrated for only a few compounds to date – one class of compounds being the flavonoid glycosides that are present in many aerial parts of herbal medicines. Quercetin glycosides such as hyperoside (quercetin-3-O-β-D-galactopyranoside) and isoquercitrin (quercetin-3-O-β-D-glucopyranoside) are often present in the diet together with numerous other naturally occurring flavonoids [69,70]. Though flavonoids present with low bioavailability of around 35%, extensive metabolism to phenolic compounds (such as phenylacetic acid derivatives) and recycling of glycosides, glucuorindes, and sulfates takes place in the intestines by gut bacteria. Glycosides are initially hydrolyzed by gut bacteria to the respective aglycone which is able to be absorbed into enterocytes through passive absorption. Glycosides themselves, however, can be actively transported into enterocytes by sodium glucose transporter protein 1 (SGLT1) which is a common transporter for mono- and disaccharides [71]. The glycosides are then removed from enterocytes either by passing into the portal vein or back into the intestinal lumen via MDR proteins. Metabolism in enterocytes leads to deglycosidation to the aglycone and conjugation to glucuronide or sulfate metabolites via sulfotransferases and UDP-glucuronosyltransferases. The resulting conjugated metabolites are then either entering the portal vein blood, the bile, or are transported back into the intestinal lumen via MDR. Both glucuronides and sulfates can undergo bacterial degradation to the respective aglycone again [70]. The ability of intestinal bacteria to further metabolize the flavonoid aglycone to phenolic compounds provides new insights into the metabolic profile of these and many other compounds [72]. The important role of hydrolysis of conjugated metabolites back to their respective aglycones may significantly contribute to enterohepatic recirculation of many drugs [73].

Overall, the complex interactions between both the microbiome and the intestinal mucosa as well as the intestines with systemic processes such as the brain-gut axis are regulated through many processes as summarized in Figure 1.

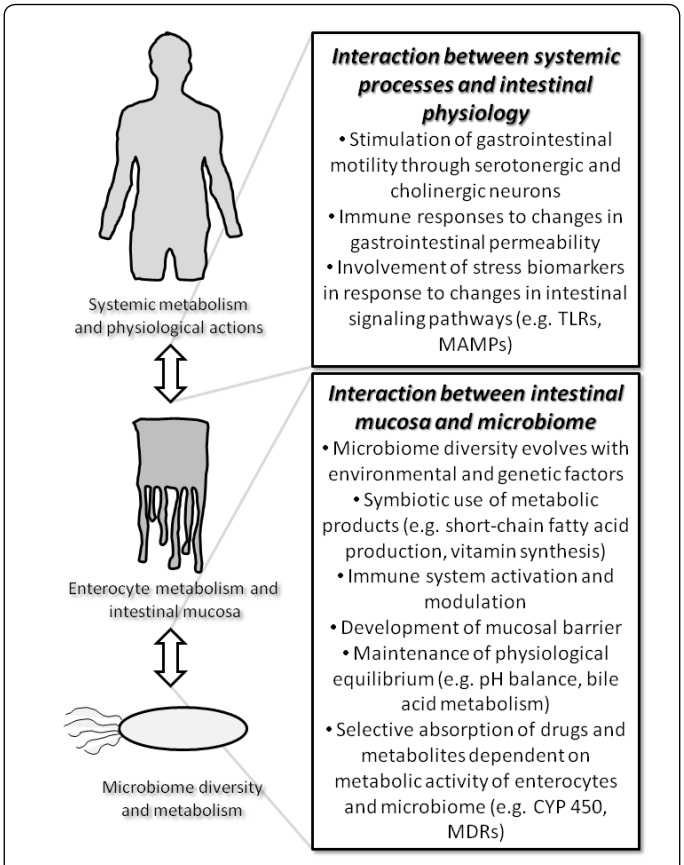

Figure 1: The complexity of metabolic interactions between the intestinal microbiome, the enterocytes and intestinal mucosa, as well as physiological processes in the body.

Pharmacokinetic and toxicokinetic consequences of microbial drug metabolism and new approaches to drug design

Although the influence of metabolic processes by the microbiota has been known for many decades, interest in pharmacokinetic and toxicokinetic influences on drug metabolism have just recently resurfaced and are now considered a new stepping stone in the drug development process [73]. While preclinical and clinical data are still sparse, there is a growing body of evidence suggesting particular metabolic reactions that are exclusively performed by gut microbes either to the benefit or to the detriment of the host [11]. There are a number of examples where absorption and metabolism are influenced and sometimes even necessary components of bioactivation of toxification of drugs. An example of bioactivation is the reductive metabolism of salazine compounds for the treatment of ulcerative colitis and other inflammatory bowel disorders. It had been discovered that prontosil and neoprontosil, pro-drugs of sulfanilamide, are exclusively metabolized in the large intestines to release the active sulfanilamide drug [56]. This reductive metabolism was later applied to aminosalicylic acid pro-drugs such as olsalazine which resulted in anti-inflammatory effects in the gut as well as absorption and excretion of the corresponding coupling agent and the salicylic acid derivative [74]. Bioactivation pathways are an example of beneficial effects of microbial metabolism but in some cases, metabolic activity may also lead to generation of toxic metabolites with local and systemic effects. One example is the reduction of nitrazepam by microbiota in the rat and human intestinal tract to 7-aminonitrazepam which is then further metabolized in the liver after

absorption to the teratogenic metabolite 7-acetylaminonitrazepam [58]. Another notable toxicity due to bacterial metabolism in the intestines is related to bone marrow aplasia of a metabolite of the antibiotic chloramphenicol. This metabolite is only generated by a small percentage of patients who take the drug orally and have a high percentage of coliform bacteria that are capable of metabolizing chloramphenicol to the toxic metabolite p-aminophenyl-2-amin-1,3-propanediol [75].

Another very common metabolic reaction that has a significant impact on fecal drug excretion and enterohepatic recirculation are the deconjugation reactions occurring in the intestinal tract. A number of conjugated drugs such as digoxin, glucocorticoids, morphine, indomethacin and sex hormones are excreted with the bile as glucuronic or sulfate acid metabolites. Bacterial metabolism of these conjugates then results in generation of the aglycones or desulfated compounds that can be reabsorbed with bile acids to prolong their biological half-life [76,77].

A recent study evaluated the influence of bacterial metabolism and activity on the toxicity of the non-steroidal anti-inflammatory drug acetaminophen [23]. The ratio of glucuronide to sulfate metabolites of acetaminophen varies widely among individuals and the study was able to show that sulfation of acetaminophen in the liver competes with sulfation of p-cresol, a metabolite exclusively generated by gut bacteria. The metabolite mainly results from bacterial degradation of the amino acids tyrosine and phenylalanine. If both p-cresol and acetaminophen concentrations are high in the intestinal tract, they are absorbed without sulfation by bacteria and compete for hepatic sulfation. This highlights the importance of competing metabolic routes for detoxification of compounds. While acetaminophen is considered a very safe drug to use, there is a small patient collective that is susceptible to developing hepatotoxicity at much lower doses than the general population [78]. A number of other drugs that are mainly metabolized through phase II sulfation pathways and could potentially be presenting with similar issues are minoxidil, tamoxifen, and apomorphine, among others.

Such data suggest that intestinal metabolism can significantly impact drug metabolism and toxicity. As of yet, only isolated studies have been conducted to further elucidate the consequences of gut microbial metabolism and how such studies may actually benefit the drug development process in designing better pro-drugs that are absorbed from the gastrointestinal tract in a controlled and optimized manner [16,47,57,68,71,79]. Several initial approaches have been made to provide a better understanding of the metabolic diversity of the microbiome as illustrated by the examples given above. However, further research into the metabolic capabilities of gut microbiota may result in better prediction of oral bioavailability models as well as specifically designing drugs to avoid variability in oral absorption through metabolic processes. These are challenging goals since the human microbiome is highly diverse and there is significant variability between different ethnic groups and in different environments. Former approaches have focused on the detection of radio-labeled or fluorescent compounds and their metabolites both in the intestines and after absorption in animals and humans [80,81]. Such approaches, though useful in providing insights into the absorption and distribution of drugs after oral application, do not consider the intestinal metabolism. One obstacle that appears to hinder progress in this area is the complexity of the interaction between bacterial and host metabolic processes as well as the interindividual variability in metabolic activity and microbiome composition. With the emergence of more sophisticated tools such as metabonomics and gene sequencing such obstacles can be overcome and allow for a more comprehensive picture of both intestinal drug metabolism and mechanisms of toxicity.

Similar to the current FDA guidelines concerning the generation of reactive metabolites (human metabolites in safety testing) based on structural features [82] it may prove beneficial to evaluate certain drug properties that may predispose a structure for microbial metabolism.

Conclusion

A renewed interest in the complex and intricate interactions between intestinal microbiome and human drug metabolism is offering interesting findings and opens new pathways for drug development. Considering that the symbiosis between microbes and host are fine-tuned by the brain-gut axis as well as influenced by environmental and genetic factors, the use of metabonomics and hyphenated techniques can aid in identifying specific metabolic pathways. Especially in the drug development process, a better and more detailed understanding of potential intestinal metabolic pathways and how they are catalyzed or influenced by the gut microbiome may aid in a more targeted drug design as well as reduce potential side effects or drug interactions. The unique evolution of host-microbiome interplay can be utilized for targeted and individualized drug delivery as well as aid in the understanding of disease conditions that are often associated with metabolic changes.

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