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The Role of the Gut Microbiota in the Toxicity of Food-Borne Chemicals

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ABSTRACT

Growing evidence indicates that the human gut microbiota interacts with xenobiotics, including food borne chemicals and persistent organic pollutants. The toxicological relevance of the gut microbiota-pollutant interplay is of great concern since chemicals may disrupt gut microbiota functions, with a potential impairment of host homeostasis. Humans ingest a multitude of small molecules that are foreign to the body (xenobiotics), including dietary components, environmental chemicals, and pharmaceuticals. The trillions of microorganisms that inhabit our gastrointestinal tract (the human gut microbiota) can directly alter the chemical structures of such compounds, thus modifying their lifetimes, bioavailabilities, and biological effects. Our knowledge of how gut microbial transformations of xenobiotics affect human health is in its infancy, which is surprising given the importance of the gut microbiota. We currently lack an understanding of the extent to which this metabolism varies between individuals, the mechanisms by which these microbial activities influence human biology, and how we might rationally manipulate these reactions. This deficiency stems largely from the difficulty of connecting this microbial chemistry to specific organisms, genes, and enzymes.

Keywords: Food-borne chemicals, Antimicrobials, Silver nanoparticles, Gut microbiota, Xenobiotics.

INTRODUCTION

The human gut microbiota is a dynamic ecosystem formed by a pool of 400–1000 adherent and non-adherent bacterial species belonging mostly to two dominant phyla, the Firmicutes and the Bacteroidetes [1]. Although the composition of an adult microbiota remains relatively stable, it is well known that the microbial diversity is acquired very early in life within the first hours post birth, and is shaped over time as the diet becomes more complex and the immune-system matures. Hence, the combination of multiple factors including genotype, mode of delivery, early antibiotic therapy, diet composition, lifestyle, social interactions and environmental exposure to various xenobiotics shape the gut microbiota to make every individual microbially unique [2] [3]. This is of importance because the gut microbiota fulfills many critical roles in essential host functions such as protection against pathogens, immune-system modulation, fermentation of nondigestible dietary fibres, anaerobic metabolism of peptides and proteins, interaction with the host's circadian clock and biotransformation of xenobiotics [4] [5]. Such a complex symbiotic interaction is the result of a remarkable metabolic activity driven by a genetic pool whose size is a hundred times larger than the human one.

Over the past several decades, studies of gut microbiota–mediated modification of xenobiotics have revealed that these organisms collectively have a larger metabolic repertoire than human cells. The chemical differences between human and microbial transformations of ingested compounds arise not only from the increased diversity of enzymes present in this complex and variable community but also from the distinct selection pressures that have shaped these activities [6]. For example, whereas host metabolism evolved to facilitate excretion of many

xenobiotics from the body, microbial modifications of these compounds and their human metabolites often support microbial growth through provision of nutrients or production of energy. Notably, the chemistry of microbial transformations often opposes or reverses that of host metabolism, altering the pharmacokinetic and pharmacodynamic properties of xenobiotics and associated metabolites.

The range of xenobiotics subject to gut microbial metabolism is impressive and expanding. Gut microbes modify many classes of dietary compounds, including complex polysaccharides, lipids, proteins, and phytochemicals [7]. These metabolic reactions are linked to a variety of health benefits, as well as disease susceptibilities. Gut microbes are also able to transform industrial chemicals and pollutants, altering their toxicities and lifetimes in the body. Similarly, microbial transformations of drugs can change their pharmacokinetic properties, be critical for pro-drug activation, and lead to undesirable side effects or loss of efficacy. In the vast majority of cases, the individual microbes and enzymes that mediate these reactions are unknown.

Fueled by findings underscoring the relevance of microbial xenobiotic metabolism to human health, scientists are increasingly seeking to discover and manipulate the enzymatic chemistry involved in these transformations [8]. Exploring how gut microbes metabolize the drugs digoxin and irinotecan, as well as the dietary nutrient choline, provides guidance for such investigations. A molecular understanding of gut microbial xenobiotic metabolism can guide hypothesis-driven research into the roles these reactions play in both microbiota and host biology.

Antimicrobial Silver Nanoparticles

In the case of antimicrobial silver nanoparticles with application in food industry, the main human exposure source is through the oral-gastrointestinal tract [9]. The mean dietary exposure level of Ag-NPs is estimated at 70–90 _g/day [10]. After ingestion, the Ag-NPs come in contact with lumen of the oral cavity and esophagus. There is little published information on the absorption rate of particulates through the epithelium of these two compartments, probably due to both a low surface area and a short residence time for most food matrices [11]. After that, during the gastrointestinal digestion process in the stomach and small intestine, the interaction of Ag-NPs with biological fluids can lead to its agglomeration, aggregation, and dissolution [12] [13].

In addition, silver nanoparticle absorption (transcellular and paracellular transport and vesicular phagocytosis) through the gastrointestinal tract epithelium could take place. Finally, the nanoparticles that escape the absorption process reach the colon where they could modulate the composition and/or activity of gut microbiota, affecting the production and toxicity of bacterial metabolites [14]. Part of the initial intake of nanoparticles could be extracted in feces. According to the anatomy of the gastrointestinal tract, several environments characterized by specific microbiota composition are found. Gut microbiota harbors more than 100,000 billion microorganisms, including bacteria, fungi, viruses, protozoa and archaea, with bacteria representing a majority.

The dominant gut bacterial phyla are the Firmicutes (including Clostridium, Enterococcus, Lactobacillus, and Ruminococcus genera) and Bacteroidetes (including Bacteroides and Prevotella genera). These bacteria play an important role in the development and conservation of host health. Gut microbes play a role in human physiology through several mechanisms, including their contribution to nutrient and xenobiotic metabolism (e.g. synthesis of vitamins, digestion of oligo, and polysaccharides, drugs, etc.) and to the regulation of immune and neurodendocrine functions. Some of these effects are mediated by products of bacterial metabolism, such as short-chain fatty acids (SCFA), including propionate, butyrate or acetate, which influence the gut barrier, the inflammatory tone and the metabolic homeostatic control in different tissues [15].

To date, little is known about the effect of nanoparticles on the intestinal microbiota, but what is known is that there are numerous factors that can produce an imbalance in the intestinal bacterial populations, like food, triggering certain diseases. That is why the investigation of the NPs-gut microbiota relationship is so important and should continue [16], [17]. The physical and chemical transformations of Ag-NPs during the gastrointestinal digestion could involve modifications in their toxic effect. Despite the specific features of these particles and the differences among them, they all display a close relationship between physicochemical reactivity and bioavailability/biopersistence in the gastrointestinal tract.

Arsenic

Arsenic is a ubiquitous environmental contaminant present in its trivalent or pentavalent state in both organic and inorganic compounds. Human exposure occurs primarily by consumption of contaminated fish and crustaceans. Chronic exposure is associated with the development of bladder, liver, kidney and lung cancers [18] [19]. The reduction of arsenic acid (iAsV) to arsenous acid (iAsIII) by rat caecal bacteria has been reported. In human, iAs is sequentially methylated and predominantly excreted as dimethylarsinic acid. This methylation process was originally considered to be a detoxification process but the formation of highly reactive methylated intermediates (monomethylarsonous acid MMAIII and dimethylarsinous acid DMAIII) has led to reconsider methylation as an activation process.

Rodent and human gut microbes methylate iAs to monomethlyarsonic acid (MMAV), monomethlyarsonous acid (MMAIII)and monomethylmonothioarsonic acid (MMMTAV). The methylation of arsenic by GI bacteria has long been thought to have a small contribution to the overall methylation process in vivo, because iAsV and iAsIII are rapidly absorbed in the small intestine. However, soil- and/or dietary-bound arsenic may be digested differently: Van de Wiele *et al.*, have shown that human colonic microorganisms can also methylate arsenic in arsenic-contaminated soils in vitro.66 However, there is still no direct evidence that the microbial metabolism of arsenic is of toxicological significance for the host.

Artificial Sweeteners

Artificial sweeteners were introduced into the human diet more than a century ago to decrease caloric intake and are now widely found in commonly consumed foods such as diet soft drinks and food. The impact of artificial sweetener consumption on health is a matter of intense debate. Some studies have shown benefits of their consumption, whereas others have suggested associations with increased risk of type 2 diabetes. Cyclamate is one of the most widely used artificial sweeteners in Europe [20] [21]. It is metabolized into cyclohexamine, which is thought to be responsible for the carcinogenic effect of cyclamate, an effect that resulted in the banning of cyclamate in the UK and the US, although this toxicity is still controversial [22].

Interestingly, cyclamate metabolism is inducible. Cyclohexamine was detected as the main urinary metabolite of 14C-cyclamate in rats, rabbits, guinea pigs and humans, and in individuals chronically consuming cyclamate before administration of the radio labelled dose. Evidence implicating the GI microbiota as the site of cyclamate metabolism are numerous [23]. Cyclamate was found to be converted to cyclohexamine in vitro by the contents of the lower gut but not by the tissues of rats pretreated with cyclamate;80 rats given cyclamate in drinking water for several months became ‘converters’, excreting cyclohexamine, but this ability to convert cyclamate was lost when antibiotics were added to water.81 Many publications have extended these observations to humans, providing evidence that the GI microbiota is the sole site of cyclamate metabolism [24] [25].

CONCLUSION

The GI bacteria have broad enzymatic capacities and can metabolise food-borne chemicals from various chemical families, either increasing or decreasing their

toxicity to the mammalian host. Conversely, food-borne chemicals may also affect the composition and/or optimal function of the GI microbiota, with potential effects on the health of the host. Overall, GI microbiota represent a major player in the toxicity of food-borne chemicals. Nevertheless, there remain many challenges to overcome in order to establish the level of risk associated with food-borne chemicals in interaction with gut bacteria.

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