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The bidirectional interaction between our gut flora and drugs

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Abstract

The term "pharmacogenetics" refers to the study of individual genetic variations that give rise to different responses to the intake of a drug. Recently, however, it has begun to think that an important role in this sense can also be played by our microbiota. The interaction between our gut microbial flora and drugs is actually bidirectional: evidence has accumulated that some drugs, in addition to classical antibiotics, have a strong impact on the composition of the microbiota.

Keywords: microbiota, drugs

1. Introduction

The term microbiota refers to the millions of billions of microorganisms (bacteria of thousands of different species, *Archaea*, viruses, and fungi that crowd our organism). These microbes live on the skin, in the mucous membranes of the mouth, in the respiratory tract, but a particularly important role is played by the intestinal component, a diverse and dense microbial community, unparalleled in other bodily habitats. At birth, the digestive tract is almost sterile: the intestinal microbiota is transferred from the mother to the child during childbirth, when it occurs naturally, and this process of colonization continues during the first days of life, with different species depending on whether the infant is artificially or breastfed. It then undergoes a prolonged period of postnatal development, during which it is influenced by contact with external agents such as foods, metals, and toxic substances.

It is estimated that the intestinal bacterial heritage of an adult is composed of over one hundred trillion cells, most of which belong to six bacterial phyla: *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia.* They perform functions essential to our health, such as the breakdown of plant polysaccharides - fibers - indigestible by the host, the detoxification of xenobiotics, substances foreign to the body, the suppression of the growth of harmful microorganisms by competitive exclusion and the development of the host immune system, the biosynthesis of essential vitamins and amino acids. For example, our organism is unable to produce vitamin K, which is essential for the proper synthesis of coagulation factors, and uses, in addition to the diet, that which is produced by some bacteria of our resident intestinal microbial flora.

The healthy pulmonary microbiota contains many commensal bacteria derived from the upper respiratory tract, mainly belonging to the phylum *Bacteroidetes*, especially the genus *Prevotella*, and the phylum *Firmicutes*, especially *Veilonella* and *Streptococcus* (Dickson et al. 2015). Its composition is determined by numerous factors and anatomo-clinical circumstances: a) displacement of bacteria from the upper airways by passive migration, b) gastroesophageal micro-aspiration from the digestive tract c) saprophytic anti-infective activity by the innate and adaptive defenses of the healthy lung, d) by

productive catarrhal cough and altered mucociliary clearance that modulate pathological cellular and bacterial migration (Dickson and Huffnagle 2015).
The healthy lung microbiota acts as a guardian of respiratory health by providing local immunologic defense factors that prevent colonization of opportunistic pathogens by triggering eosinophilic and/or neutrophilic cellular inflammatory processes (Dekaboruah et al. 2020). The dramatic disruption of this respiratory commensal flora (termed pulmonary dysbiosis) in patients with chronic lung disease alters the physiological taxonomic composition resulting in acute inflammation that has been associated with the chronic inflammatory pathogenesis of lung disease.
The balance between our organism and the bacterial flora that inhabits it is therefore valuable, but the composition of the microbiota is highly dynamic and shows substantial inter-individual and intra-individual variations. It is closely related to the age and genetics of the host, but also to environmental factors such as season, smoking, number of hours of sleep, even consumption of carbonated beverages and type of diet (Falony et al. 2016).

2. *How drugs interact with intestinal microbiota*

Evidence has accumulated that some drugs, in addition to classical antibiotics, have a strong impact on the composition of the microbiota.
With few exceptions, drugs do not see their site of action in the intestine but, if they are administered orally, they reach it to be absorbed there and then distributed, thanks to blood-mediated transport, throughout the body. Naturally, it is difficult to determine precisely how much drug will reach the site of action and how long it remains there. Also, for this reason it is difficult to determine what effect it may have on the resident intestinal flora and vice versa.
While it is easy for antibiotics to understand how they can alter the composition of the intestinal flora depending on their spectrum of action, it was more surprising to see evidence of a bactericidal effect on many non-antibiotic drugs. A study published in 2018 analyzed about a thousand non-antibiotic drugs and showed that 24% of them, including mostly agents used in the treatment of mental disorders, antidiabetics, and anticancer agents and inhibited, in vitro, the growth of representative strains of bacterial flora (Maier et al. 2018).
Alterations in the composition of the intestinal flora are linked to mental disorders such as anxiety, schizophrenia, bipolar disorder and depression. Drugs used to treat these illnesses have been found to interact significantly with the microbiota. The first marketed antidepressant, iproniazide, a monoamine oxidase inhibitor, is now used as a drug to treat tuberculosis due to its ability to kill the mycobacterium responsible.
Some widely used antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), have been shown to inhibit the efflux pumps of bacteria and thus prevent their replication. Phenothiazines (and some derivative molecules used as antihistamines), the largest class of antipsychotics, have also been associated with anti-infective properties. In this regard, that of antipsychotic drugs is a particularly interesting chapter: numerous studies have been conducted on their interaction with the bacterial flora, and it has been shown that the administration of atypical antipsychotics as recently introduced psychotropic drugs that are more tolerated than their predecessors, induces dysbiotic alterations to the composition of the intestinal microbiota. Interestingly, there is an inverse relationship, as antibiotic-induced dysbiosis has been linked to mental disorders such as anxiety and depression (Mognetti 2020).
It has been proposed that many of the metabolic side effects associated with the use of atypical antipsychotics, including weight gain, cardiometabolic disorders, and development of the metabolic syndrome, are the result of pharmacological action on the microbiota. For example, long-term exposure to risperidone increases the *Firmicutes/Bacteroidetes* ratio, which is associated with obesity. In addition, a decrease in *Akkermansia muciniphila* has been observed in patients treated with atypical antipsychotics, and this species is known to have beneficial anti-inflammatory effects and to adversely affect fat mass development. An experimental study in mice lacking bacterial flora (germ-free) then revealed that the gut microbiota was responsible for the weight gain observed in response to olanzapine treatment. Similarly, the side effects of these drugs on metabolism were partially re-

versed in female rats when administered concomitantly with an antibiotic (Flowers et al. 2017). Taken together, these results demonstrate that atypical antipsychotics can have a profound impact on host metabolism through their effects on the gut microbiota.

Sometimes the effect of the drug on the composition of the intestinal flora is indirect. Proton pump inhibitors (gastroprotective drugs widely used, for example in the treatment of gastric ulcer or gastroesophageal reflux diseases) modify the pH of the gastrointestinal tract, thus favoring the proliferation of bacterial species that prefer a more basic environment to the detriment of those that prefer an acid environment. Proton pump inhibitor users have been shown to have a larger bacterial flora consisting of more species than non-users (Imhann et al. 2016; Jackson et al. 2016).

The list of non-antibiotic drugs capable of modifying the composition of the intestinal microbiota is long, and includes, among others, hormonal contraceptives, laxatives and antihistamines. However, in many cases we do not know how this happens and if the impact is relevant for the whole flora or only for some bacterial species, also considering other parameters such as contact times and the amount of drug that actually remains in the intestine (Mognetti 2020).

3. Microbiota action on active drugs

Some drugs can modify the composition of the bacterial flora, but numerous studies have shown that contextually, it is capable of modifying many of the active ingredients of the drugs with which it comes into contact, similar to what it is able to do on molecules that we normally introduce with food (Kåhrström, Pariente, and Weiss 2016). Several drugs that can be modified by the gut microbiota have already been identified, including omeprazole, a gastroprotectant, clonazepam, an anxiolytic, the antidiarrheal loperamide, and many others. The list of drugs subject to modification by the intestinal flora is certainly incomplete, since systematic analyses on microbial metabolism are still lacking, also in light of the great inter- and intra-individual variability of the bacterial flora.

A documented example in which the action of a bacterium component of our intestinal microbiota negatively affects the effect of a drug is *Eggerthella lenta*, a bacterium known to possess an enzyme by which it inactivates digoxin, a valuable drug of plant origin used to treat heart failure.

Similarly, other rations that certain bacterial species perform on specific drugs have been identified. Except in rare cases, however, we do not know whether these reactions modify the effect of the drug and in what way. It is possible that bacterial-induced changes in vivo enhance the effect of the drug, in which case they would be beneficial to the user. Or they could be responsible for certain collateral effects, a hypothesis that has been put forward especially for drugs that have repercussions at the gastrointestinal level or that, as in the case of some antipsychotics, cause an increase in body weight. In this sense, is paradigmatic the case of irinotecan, an anticancer drug that our body binds to a molecule called glucuronic acid in order to eliminate it more easily. The complex irinotecan-glucuronic acid, in addition to being less toxic than the original drug, is also more easily removed with the feces. Some bacteria in our intestinal flora are equipped with an enzyme, beta-glucuronidase, which can break down the bond between the drug and the cofactor, thus returning the drug to its original form and toxicity.

Therefore, given the ability of our commensal bacteria to modify the drugs that transit in our intestine, it was thought to intervene on these reactions, to limit them when they are harmful or to exploit them when they are favorable to the host. For example, with reference to the case of irinotecan, researchers have found a way to prevent the activity of beta-glucuronidase with inhibitors that do not modify the composition of the bacterial flora nor give an effect on our organism. This would allow the anticancer drug to be administered while limiting its toxicity. Other interventions have been devised in this sense: for example, it has been demonstrated that modifying through probiotics or antibiotics the composition of the bacterial flora by including some species of gram-positive bacteria, influences the effectiveness of the antineoplastic drug cyclophosphamide (Mognetti 2020).

4. Conclusions

Many studies are focusing on the potential of microbiota-based medicine. Continued advances in the field could lead to targeted approaches to improve drug outcomes by modifying the gut bacterial makeup and to have drug outcomes predicted based on the composition of everyone's flora. However, it will not be easy to incorporate the role of our bacterial flora into toxicology and pharmacology: drug-microbiota-host interactions are inherently complicated and as such require a complex combination of experimental and computational approaches to dissect them. In any case, developing tools, including dietary, or even synthetically engineered probiotics and bacteria through which to manipulate the microbiota for therapeutic purposes would allow us to better respond to a drug or limit its side effects.

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