Macedonian pharmaceutical bulletin, 68 (Suppl 1) 543 - 544 (2022)
Online ISSN 1857 - 8969
DOI:10.33320/maced.pharm.bull.2022.68.03.260
Short communication

Gut microbiota metabolism and bioaccumulation of drugs

Maja Đanić[1*], Slavica Lazarević[1], Nebojša Pavlović[2], Bojan Stanimirov[3], Momir Mikov[1]

[1]*Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine, University of Novi Sad, Hajduk Veljkova 3, 21000 Novi Sad, Serbia*
[2]*Department of Pharmacy, Faculty of Medicine, University of Novi Sad, Hajduk Veljkova 3, 21000 Novi Sad, Serbia*
[3]*Department of Biochemistry, Faculty of Medicine, University of Novi Sad, Hajduk Veljkova 3, 21000 Novi Sad, Serbia*

Introduction

Gut microbiota is a complex ecosystem composed of various microorganisms, mostly bacteria, that mediate the interaction of the human host with their environment and have a huge impact on the overall human health. The composition of gut microbiota is relatively stable throughout the life. However, a number of factors have been associated with variability in microbiota composition or function, including diet, stress, sex hormones, different xenobiotics, environmental toxicants and the number of drugs consumed such as antibacterial agents or proton pump inhibitors. Emerging evidence suggests that these factors mutually shape the gut microbiome throughout an individual's lifespan, resulting in a unique and personalized microbial fingerprint. It has been shown, that disturbances in gut microbiota composition and function are associated with many chronic diseases, from gastrointestinal to different systemic diseases. The role of intestinal bacteria in therapeutic outcome of patients to drugs has recently become the subject of extensive research, due to high metabolic capacity and interindividual variations in composition that may be the consequence of unpredictable response toward drug therapy (Li et al., 2016; Stojančević et al., 2014; Weersma et al., 2020).

Therefore, the aim of the current review is to summarize and elucidate the role of the gut microbiota in drug metabolism and bioaccumulation and the consequences of these interactions.

Materials and methods

A literature search was carried out in the PubMed database searching through original and review articles, published from 2010-2022. A following combination of keyword has been used: gut microbiota, drug metabolism, drug bioaccumulation, drug biotransformation.

Results and discussion

Drug metabolism by host tissues, such as the liver, has been well studied. The role of intestinal microbiota in this process is still insufficiently explored, but essential, field of study in pharmacology and toxicology. As the gut microbiota encode a substantively larger number of genes than its human host, it is obvious that they are able to undertake a variety of metabolic functions that humans are unable to do or are only able to do in a limited capacity. In addition to metabolism of nutrients and endogenous substances such as bile acids and vitamins, intestinal bacteria play a crucial role in biotransformation of many xenobiotics. To date, at least 30 commercially available drugs have been shown to be substrates of gut microbes-derived enzymes, and an increasing number of drugs may have the potential to contact with the distal gut. Drugs which are good candidates to interact with gut microbiota are those that are orally administered but have low solubility, low permeability or both and thus reach the lower parts of gastrointestinal tract where the number of bacteria is the highest (Li et al., 2016; Stojančević et al., 2014; Weersma et al., 2020).

*maja.djanic@mf.uns.ac.rs

Metabolism of drugs by gut microbiota

The metabolism of drugs by gut microbiota prior to absorption can alter the systemic bioavailability and overall therapeutic outcome of certain drugs. Contrary to liver which is mainly responsible for metabolism *via* oxidation and conjugation, intestinal bacteria are mostly involved in reductive and hydrolytic reactions. Among them, hydrolytic enzymes including β-glucosidase and β-glucuronidase are the most predominant and exhibit the strongest activities across bacterial species. The most commonly enzyme activities mediating reduction are azo-reductase, nitro-reductase, and nitrate reductase. Additionally, the intestinal bacteria express enzymes involved in reactions of decarboxylation, dehydroxylation, dealkylation, dehalogenation, deamination as well as in metabolism of glutathione conjugates. Biotransformation of drugs by intestinal bacteria may lead to drug activation, drug inactivation, increased toxicity of drugs because of reduced metabolism, altered efficacy, or adverse drug interaction (Đanić et al., 2019; Đanić et al., 2021; Li et al., 2016; Stojančević et al., 2014)

Bioaccumulation of drugs by gut microbiota

Until recently, biotransformation was thought to be the main mechanism how intestinal bacteria may affect the bioavailability of drugs. Some recent studies pointed to the new mechanism of interactions between intestinal microbiota and drugs - drug bioaccumulation in bacteria. Drug bioaccumulation by bacteria refers to bacteria storing the drug intracellularly without chemically modifying it, and in most cases without the growth of the bacteria being affected (Cohen and Kelly, 2022; Klünemann et al., 2021; Đanić et al. 2019). In a recently published study, scientists from the University of Cambridge revealed that some common drugs such as antidepressant duloxetine, can accumulate in gut bacteria altering bacterial function that consequently may reduce the drug effectiveness. On the other hand, certain drugs, such as montelukast and roflumilast, can both be bioaccumulated and biotransformed by intestinal bacteria (Klünemann et al., 2021).

Conclusion

To summarize, the gut microbiota is another metabolically active compartment in human body together with classical drug metabolism in the liver that affects the safety and effectiveness of drugs. In addition, implication of gut microbiota may be achieved through the bioaccumulation of different drugs that may also alter drug availability, pharmacokinetics and overall therapeutic outcome in patients. Although the implication of gut microbiota to drug pharmacokinetics and toxicity is increasingly recognized, it still remains largely unexplored area due to the extremely complex relationship between the gut microbiota and host. The future investigation and deeper understanding of gut microbial impacts on drug metabolism and toxicity will not only facilitate the way of personalized medicine, but also improve rational drug design.

Acknowledgements

This work was supported by the Project of Ministry of Education, Science and Technological Development, Republic of Serbia (451-03-68/2022-14/200114) and the Project of the Provincial Secretariat for Higher Education and Scientific Research (142-451-2532/2021-01).

References

Cohen, Z., Kelly, L., 2022. Bioaccumulation as a mechanism of microbiome/drug interactions. Trends. Microbiol. 30, 99-101. https://doi.org/10.1016/j.tim.2021.12.00 3

Đanić, M., Pavlović, N., Stanimirov, B., Lazarević, S., Vukmirović, S., Al-Salami, H., Mikov, M., 2021. PAMPA model of gliclazide permeability: The impact of probiotic bacteria and bile acids. Eur. J. Pharm. Sci. 1(158), 105668. https://doi.org/10.1016/j.ejps.2020.105668

Đanić, M., Stanimirov, B., Pavlović, N., Vukmirović, S., Lazić, J., Al-Salami, H., Mikov, M., 2019. Transport and Biotransformation of Gliclazide and the Effect of Deoxycholic Acid in a Probiotic Bacteria Model. Front. Pharmacol. 10, 1083. https://doi.org/10.3389/fphar.2019.01083

Klünemann, M., Andrejev, S., Blasche, S. et al., 2021. Bioaccumulation of therapeutic drugs by human gut bacteria. Nature 597, 533–538. https://doi.org/10.1038/s41586-021-03891-8

Li, H., He, J., Jia, W., 2016. The influence of gut microbiota on drug metabolism and toxicity. Li H, He J, Jia W. The influence of gut microbiota on drug metabolism and toxicity. Expert Opin. Drug Metab. Toxicol.12(1), 31-40. https://doi.org/10.1517/17425255.2016.1121234

Stojančević, M., Bojić, G., Salami, H.A., Mikov, M., 2014. The Influence of Intestinal Tract and Probiotics on the Fate of Orally Administered Drugs. Curr.. Issues Mol. Biol. 16, 55-68. https://doi.org/10.21775/cimb.016.055

Weersma, R.K., Zhernakova, A., Fu, J., 2020. Interaction between drugs and the gut microbiome. Gut 69, 1510-1519. https://doi.org/10.1136/gutjnl-2019-320204