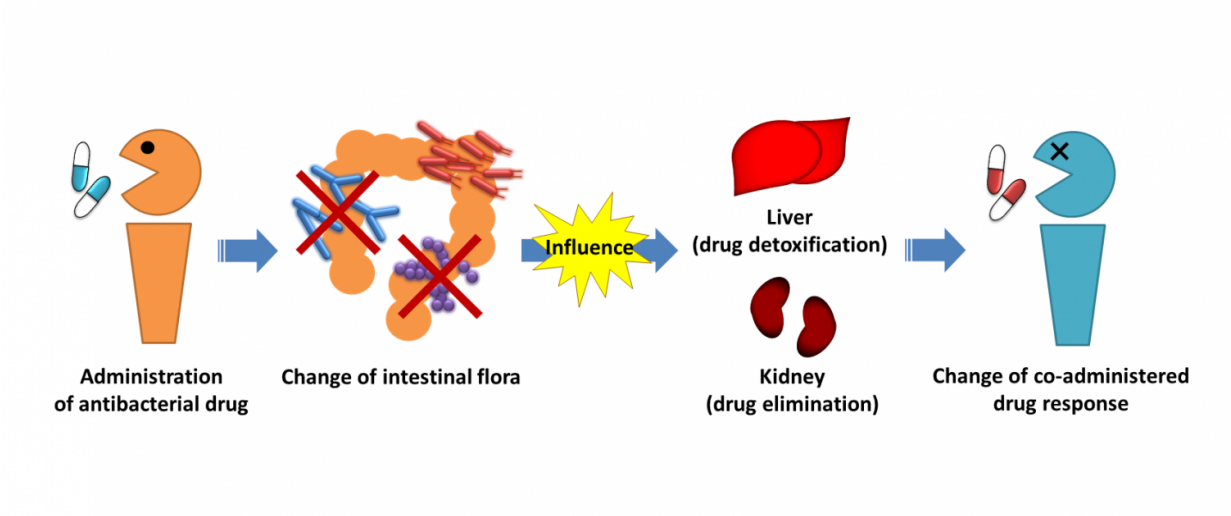
Intestinal flora effects drug response

August 12 2016



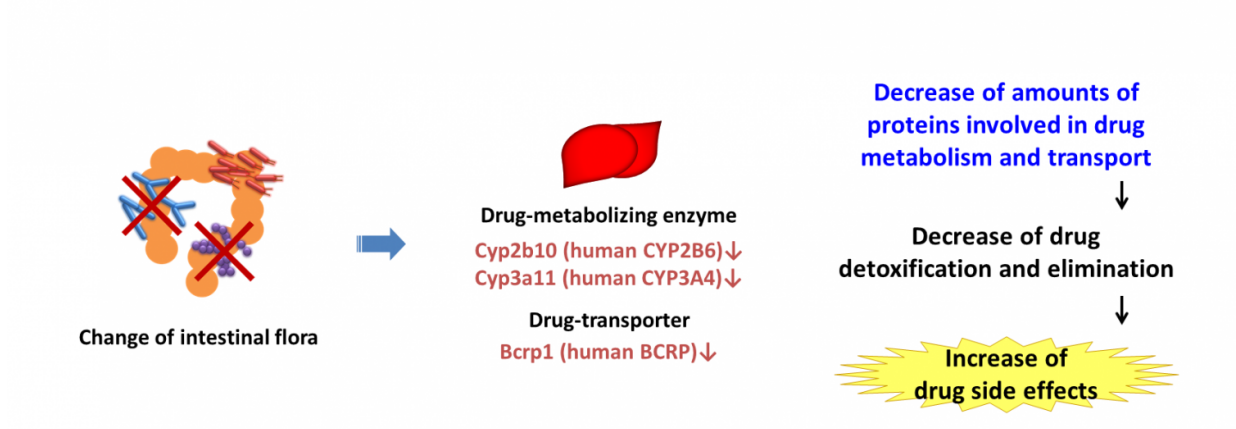
Antibacterial drugs cause changes in the intestinal flora. These changes have an influence on the capacity of the liver and kidneys to detoxify and eliminate therapeutic drugs due to large changes in the metabolizing and transport proteins. Credit: Dr. Sumio Ohtsuki

Intestinal flora has multiple influences on human health, but researchers have revealed that it is also likely to have an effect on the body's response to drugs. Recent research from Kumamoto University in Japan strongly suggests that changes in the intestinal flora, caused by antibacterial and antibiotic drugs or individual differences between people, may have an effect on a person's response to drugs including side effects. The research focused on the changes in proteins due to the condition of intestinal flora that affect the response to drugs in the liver

and kidneys.

Antibacterial and antibiotic drugs are often prescribed for the treatment and prevention of bacterial infections and are often taken with therapeutic drugs to prevent recurrence of infection during treatment. Unfortunately, the drugs affect not only harmful bacteria, but also the naturally occurring bacteria within the intestine. To determine the effects of this influence on drug efficacy, Kumamoto University researchers investigated protein changes in the liver and kidney. Changes in these proteins have a great influence on drug efficacy and side effects since they are responsible for the metabolism and transport of many drugs, and are also affected by changes in the intestinal flora.

The research was conducted using three different groups of mice, an experimental group of germ-free mice which were free of intestinal bacteria since birth, a group of mice that had received antibacterial drugs for 5 consecutive days, and a control group of mice with naturally occurring intestinal flora. Researchers used proteomics, a large-scale analysis of proteins, to clarify changes in the amount of the proteins involved in drug metabolism and transport in the liver and kidney of the two experimental mouse groups.



When the intestinal flora changes, as happens when antibiotic drugs are administered, drug-metabolizing enzymes and drug-transporting proteins are greatly reduced leading to a decreased ability to detoxify and eliminate the drugs from the system and can lead to an increase of side effects. Credit: Dr. Sumio Ohtsuki

"The most significant drug-metabolizing enzyme that decreased was cytochrome P450 2b10 (Cyp2b10)," said Professor Ohtsuki, who lead the research project. "Not only was the amount of the enzyme reduced nearly 96%, but the metabolic capacity of the drug in the liver was also reduced by approximately 82%. Cyp3a11, a similar type of enzyme was also reduced by about 88%. The human enzymes corresponding to these 2 enzymes, CYP2B6 and CYP3A4 are reported to be related to the metabolism of more than half of the pharmaceuticals on the market."

Additionally, the breast cancer resistance protein (Bcrp1), a protein that transports many kinds of cancer drugs, was reduced by more than 50% in the livers of both experimental groups. Antibacterial drugs are sometimes prescribed to treat and prevent infection caused by bone marrow suppression, a side effect of cancer drugs.

"The results of this study show that many drugs may be affected by changes in the intestinal flora," said Professor Ohtsuki. "In the future, if it is confirmed that similar mechanisms exist in humans, we expect our research to lead to optimal dosing and a reduction in drug side effects."

This finding was posted on *Molecular Pharmaceutics*, on July 5th, 2016.

More information: Takuya Kuno et al, Effect of Intestinal Flora on

Protein Expression of Drug-Metabolizing Enzymes and Transporters in the Liver and Kidney of Germ-Free and Antibiotics-Treated Mice, *Molecular Pharmaceutics* (2016). DOI: 10.1021/acs.molpharmaceut.6b00259