Cortisol controls recycling of bile acids

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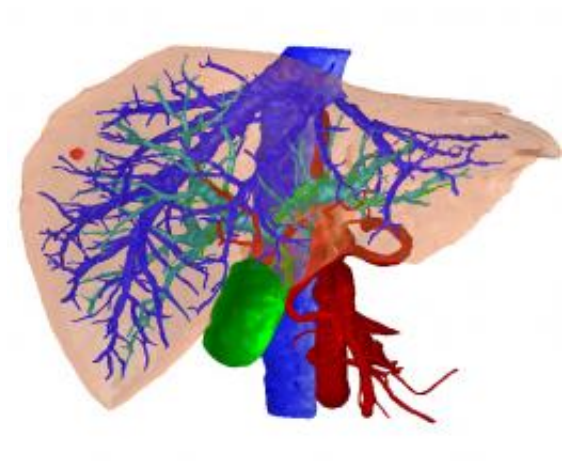

Nature sees to it that we do not have "too much choler" (bile) in our body. A delicately equilibrated regulation system ensures that there is always exactly the right amount of bile in the gallbladder. When we are hungry, our body releases a hormone called cortisol, which is a glucocorticoid. Hepatic cells receive this hormone signal through their cortisol receptors (glucocorticoid receptors) and respond by filling the gallbladder with bile in preparation of the imminent food intake. Directly upon eating a meal, bile is secreted into the intestine.

Bile acids contained in bile are indispensable for fat digestion. They emulsify fats into minute droplets, which can be broken down. Our body recovers 95 percent of bile acids from the bowel contents. They are

reabsorbed by cells of the intestinal mucosa and transported back to the liver via the blood.

"We have now found out that this recycling process is controlled by the cortisol hormone," says Dr. Stephan Herzig. Herzig is head of the Division of Molecular Metabolic Control – a joint research department of the German Cancer Research Center (DKFZ), the Center for Molecular Biology (ZMBH) of Heidelberg University, and Heidelberg University Hospitals. The research group has published its results in the journal *Cell Metabolism*. To obtain proof of cortisol's key role in bile acid recycling, the investigators used mice whose hepatic cells specifically lack the cortisol receptor. That means that cortisol signals are not received in the liver. When the modified animals were hungry, their bile contained considerably less bile acid than that of normal animals. This also led to a reduced solubility of cholesterol in the gallbladder so that an increased amount of gallstones developed. Compared to animals with intact cortisol receptor, the genetically modified mice lost weight, because they excreted fats contained in the food without digesting or using them.

The investigators also found out what causes acid levels in the bile to be reduced: In the genetically manipulated animals, transport proteins used by hepatic cells to recover bile acids from the blood have a reduced performance. As a result, bile acids remain in the blood in these mice. In the blood, however, bile acids have a hormone-like effect on various tissues. Among other things, they stimulate brown fat tissue to increase heat production.

In order to find out whether cortisol signals have an effect on bile acid recycling in humans as well, the Heidelberg scientists studied blood samples of patients suffering from a rare condition called Addison's disease. When people are affected by this disease, their immune system destroys the adrenal gland, which produces cortisol. Patients therefore

suffer from a lack of cortisol. In blood samples taken from patients before and after meals, the investigators discovered that bile acid recycling in the liver is disrupted without cortisol in humans, too.

Stephan Herzig has an idea of the possible biological purpose of the precise regulation of bile acid recycling: "The moving back of bile acid in a state of hunger is useful for protecting the body from wasting energy in times of need. If the level of bile acids in the blood is reduced under the influence of cortisol, brown fat tissue produces less heat – the body saves its energy reserves for vital functions. At the same time, this mechanism prevents gallstones from forming and ensures efficient energy intake in the intestine."

More information: Adam J. Rose, Mauricio Berriel Díaz, Anja Reimann, Johanna Klement, Tessa Walcher, Anja Krones-Herzig, Oliver Strobel, Jens Werner, Achim Peters, Anna Kleyman, Jan P. Tuckermann, Alexandros Vegiopoulos and Stephan Herzig: Molecular control of systemic bile acid homeostasis by the liver glucocorticoid receptor. *Cell Metabolism*, 2011, DOI:10.1016/j.cmet.2011.04.010

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