From metabolic health to metabolic illness: sex-specific role of hepatic ERÎ±

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Estrogens are recognized as important regulators of energy homeostasis and lipid metabolism, acting both centrally and peripherically and an impaired estrogen signalling is associated with the development of metabolic diseases. The alpha isoform of the estrogen receptor (ERÎ±) is responsible for most of estrogens' effects on energy balance and is the predominant isoform of ERs in liver. In recent years our research contributed significantly to understand the relevant role played by estrogens and ERÎ± in female liver physiology. In fact, we demonstrated that hepatic ERÎ± regulates the expression of several metabolic genes, specifically involved in cholesterol and fatty acids metabolism, ensuring a tight regulation of liver metabolism in each given reproductive stage. Epidemiological studies associate estrogen to several aspects of the metabolic syndrome. In fact, estrogen deficiency or decline in estrogen levels after menopause often leads to dysregulation of metabolism. At this point we wanted to study the hepatic function in female and male mice in normal condition and evaluate whether ERÎ± had a definite and sex-specific role in mice fed with an unbalanced diet rich of fat. To single out the role of hepatic ERÎ± on the regulation of energy homeostasis and its potential involvement in preventing metabolic disorders and the linked inflammatory state, we generated the LERKO mouse, a model in which ERÎ± gene has been selectively deleted in the liver. By studying this mouse model fed with high fat diet (HFD), model of obesity and impaired glucose tolerance, we observed that the lack of ERÎ± in the liver of LERKO female and male mice changes the sensitivity of the system, in two different ways. The presence of ERÎ± in the liver of SYNGENIC mice, the control group, makes these mice sensitive and able to answered the nutritional challenge (HFD), by tight regulation of specific pathways both in males and females. Interestingly, in LERKO mice, the lack of ERÎ± has significant and different consequences in the two sexes, mostly in HFD condition.