

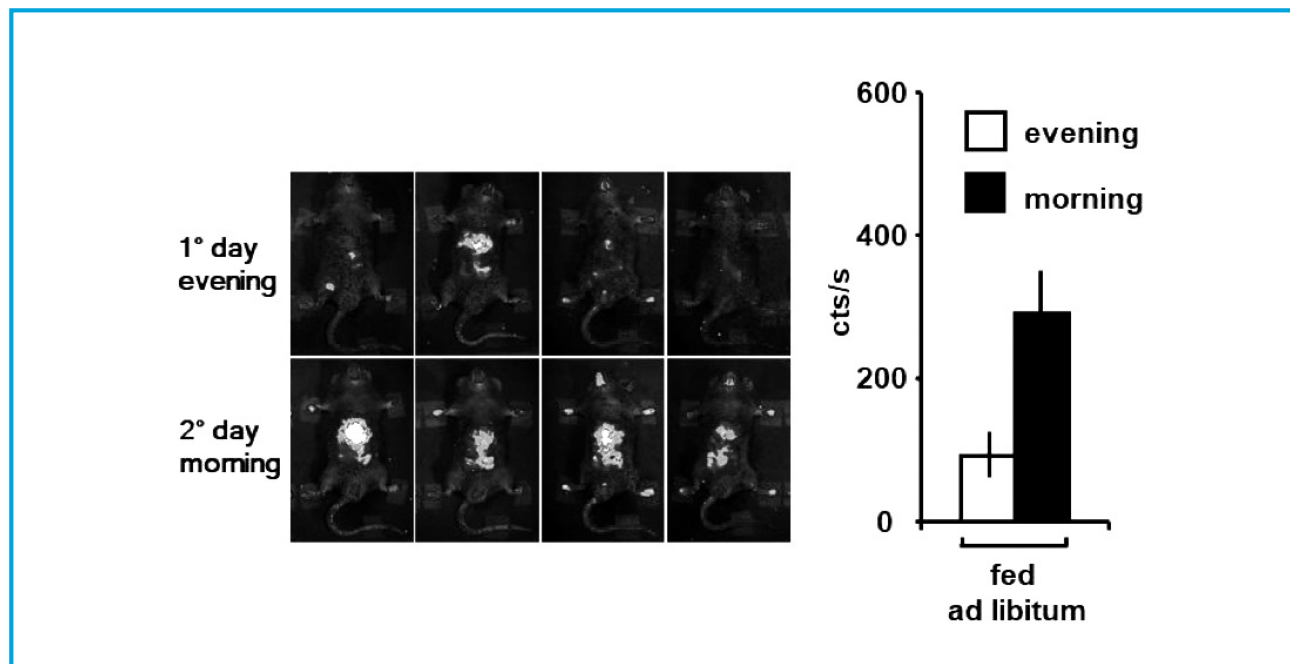
Hepatic metabolism and gender

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Our past studies demonstrated a major transcriptional activity of the estrogen receptor alpha (ER) in the liver¹; such transcriptional activity is tightly regulated by the circulating levels of estradiol and by alimentary cues^{2,3}. Further studies pointed to the liver as a sensor of the state of nutrition possibly necessary to inhibit reproductive functions in the case of famine³. Indeed, all through phylogenesis there is a major connection between reproductive and metabolic functions; the indissoluble association between the liver and the female gonads is due to the fact that most proteins indispensable for ovulation are of hepatic origin and their synthesis occur upon stimulation by estradiol, a sex steroid synthesized in the ovaries. This is very well established for oviparous species and less studied in mammals. Our finding of a strict association between gonadal functions and ER transcriptional activity in the liver has led us to further

investigate the hepatic genes modulated by this receptor in the course of the reproductive cycle. We found that in female mice ER has a major role in the regulation of lipid metabolism and transport, that appears to be adapted to the state of reproduction: lipids synthesis is negatively regulated by estrogens and changes depending of the phase of the cycle and on the state of fertility^{4,5}; these observations led us to hypothesize that with the advent of placentation and the changes in reproductive strategies occurring in mammals, the female liver had to adjust to the significant changes in energy demands associated with ovulation, pregnancy and lactation and adopt mechanisms of tight control over the hepatic energy metabolism, thus determining a major divergence from the original functions that, conceivably, were the most similar in the two sexes^{6,7}. To test this hypothesis, we carried out a series of transcriptomics



Effect of food ingestion on liver ER activity in mice. ERE-Luc reporter mice were fed ad libitum with an estrogen-free diet and bioluminescence was measured as indicator of the ER state of transcriptional activity. Bioluminescence in the liver was significantly higher in the morning when the animals were in the fed state. This observation led us to carry out a series of studies aimed at understanding which macronutrient was responsible for liver ER activation and we found that proteins, but not lipids and carbohydrates were responsible for ER transcriptional activation³.

and metabolomics analyses of the livers of adult males and females and identified major differences in the strategies utilized with regard to the response to metabolic stress. In fertile animals the female liver proved to be much more parsimonious than the male liver in the exploitation of alimentary molecules and very cautious in the generation of storage energy molecules, limiting any waste of molecules that could be precious in sustaining ovulation and pregnancy⁸. These changes in the liver metabolic strategies may explain the different susceptibility to liver and liver-associated pathologies in the two sexes and the increased incidence of these pathologies in women at the end of their reproductive cycle.

Thus these studies, underlying profound sex differences in major metabolic organ, demand further analyses with humans because they might establish the bases for novel strategies for sex-specific treatments of metabolic disorders.

Acknowledgements

This work was supported by a grant from the European Community (ERC-Advanced Grant 322977, WAYS) and by the Seventh Framework program under the grant agreement n° 278850 (INMIND).

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