Liver, dietary proteins key in fertility

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When you think about organs with an important role in reproduction, the liver most likely doesn't spring to mind. But a new report in the February issue of *Cell Metabolism*, a Cell Press publication, shows that estrogen receptors in the liver are critical for maintaining fertility. What's more, the expression of those receptors is under the control of dietary amino acids, the building blocks of proteins.

The findings in mice may have important implications for some forms of infertility and for metabolic changes that come with menopause, the researchers say.

"This is the first time it has been demonstrated how important the liver is in fertility," said Adriana Maggi of The University of Milan in Italy. "The idea that diet may have an impact on fertility isn't totally new of course, but this explains how diet, and especially a diet poor in protein, can have a direct influence."

Scientists had known that the liver expressed estrogen receptors and that those receptors played some role in metabolism. But, Maggi says, those receptors had not garnered a lot of attention.

Her group got interested in the liver receptors quite by accident. In studies of mice, "we saw that the organ that always had the highest activation of estrogen receptor was the liver," she said. Initially they thought it must be a mistake and disregarded it, but over time they began to think maybe the mice were telling them something.

They now report that the expression of those estrogen receptors depends on dietary amino acids. Mice on a calorie-restricted diet and those lacking estrogen receptors in their livers showed a decline in an important hormone known as IGF-1. Blood levels of the hormone dropped to levels inadequate for the correct growth of the lining of their uteruses and normal progression of the estrous cycle, they show.

When the calorie-restricted mice were given more protein, their reproductive cycles got back on track. Dietary fats and carbohydrates, on the other hand, had no effect on the estrogen receptors or fertility.

The researchers suggest that this connection between amino acids, estrogen receptor signaling in liver, and reproductive functions may have clinical implications. For instance, Maggi said, this may explain why people who are anorexic are generally infertile. It suggests that diets loaded with too many carbohydrates and too little protein may hamper fertility.

The results also provide new clues for understanding the increased risk of metabolic and inflammatory disease in menopausal women. Maggi says that those changes may be explained in part by the lack of estrogen action in their livers and its downstream consequences.

Today, given concerns about hormone replacement therapy, menopausal women are often treated with drugs that target one organ or another to protect against specific conditions, such as atherosclerosis or osteoporosis. Given the liver's role as a central coordinator of metabolism and producer of many other important hormones, she says, drugs that "target only the liver may solve all the problems."

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