Fertile? Not Without the Brain

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There are many causes of infertility. The fact that nerve cells can also play a role is little known. The hormone estrogen regulates the activity of neurons that give the starting signal for ovulation. Collaborating with international research groups, scientists at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have studied this signaling pathway in detail and have discovered new causes of infertility.

The time of a woman's monthly ovulation depends on how far the egg is matured and on the brain being informed about this. Estrogen, a hormone produced in the ovaries, transmits this message to the brain around the 14th day of the fertility cycle. In response, the stimulated neurons trigger increased release of another hormone called gonadotropin from the pituitary gland and, thus, give the signal for ovulation.

"The better we understand how estrogens work and what may go wrong in the interaction with neurons, the more possibilities we will have to counteract infertility," says Professor Günther Schütz, head of the Division of Molecular Biology of the Cell I at the German Cancer Research Center. Schütz and his co-workers, collaborating with Professor Allan Herbison in New Zealand and two research groups in the U.S., demonstrated that only a specific group of neurons in the brain receive the hormone signal. These cells need to have the estrogen receptor alpha in order to recognize the message and subsequently trigger production of the necessary sex hormones.

Estrogen receptors are specialized on perceiving the estrogen hormone.

Two types of estrogen receptors, alpha and beta, are found in the nervous system. It has been known that female animals suffer from lesions in the ovaries, mammary glands and uterus when they lack the estrogen receptor alpha. “Every single one of these defects is sufficient to make the animals infertile,” says biochemist Dr. Tim Wintermantel. Moreover, there were indications suggesting that estrogen receptor beta is also relevant for fertility. The scientists performed several experiments to find out more about the role played by the two estrogen receptors in the activation of neurons in the brain.

They studied mice who lacked the estrogen receptor alpha only in nerve cells. Additional estrogen given to these animals failed to trigger the hormone signal for ovulation. Furthermore, the investigators administered synthetic molecules developed and provided by Schering AG, Berlin, to healthy female mice. These substances activated exclusively the estrogen receptor alpha. This alone was sufficient to increase hormone production substantially. “Both experiments led to corresponding results,” explains Tim Wintermantel. “The estrogen receptor alpha needs to be not only present but also activated.”

Nevertheless, a gap in the researchers’ model became apparent: The neurons that are critical for the release of the messenger substance gonadotropin do not have the estrogen receptor alpha. How do the gonadotropin producers receive the signal to increase hormone release if they are unable to receive the estrogen message? The researchers discovered that a second group of neurons in the hypothalamus transmits the message. They demonstrated that these mediators are equipped with the alpha antenna and that they use long cellular extensions to connect with the cells that induce gonadotropin production in the pituitary gland.

Günther Schütz is convinced that this regulatory cycle is not the only one that estrogen uses to control the activity of neurons. “This could be important, for example, for patients who lack a specific receptor on the

gonadotropin producing cells and who are infertile because of this," he says. Therefore, the medical researcher plans to investigate further signaling pathways of estrogen in the brain with his co-workers in future.

Source: German Cancer Research Center