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Press information

Towards Understanding the Origin of the Most Common Form of Female Infertility

Researchers from Inserm and Université de Lille have discovered that the most common female infertility disorder - polycystic ovary syndrome (PCOS) - may be caused by overexcitation of brain neurons. The culprit? A hormone produced by the ovaries, called "anti-Müllerian hormone" (AMH), which is produced in excess in women with PCOS. Research conducted by the team in mice show the importance of *in utero* exposure to abnormally high levels of AMH in the occurrence of the disease. These findings, published in [Nature Medicine](#), pave the way for new concepts linked to the embryonic origin of the disease as well as new avenues for the development of a treatment.

One in ten women of childbearing age suffers from polycystic ovary syndrome (PCOS), in which the ovaries produce androgens (male hormones) in excess, disrupting the growth mechanisms of the ovarian follicles. A greater number of these follicles will stagnate - hence the (erroneous) term "polycystic ovaries" - leading to ovulation dysfunction responsible for infertility.

While we currently know how to diagnose the disease, its cause remains unknown. Current therapeutic options aim to reduce symptoms and prevent complications but no preventive or curative treatment exists.

A team coordinated by Paolo Giacobini, Inserm Research Director (Jean-Pierre Aubert Research Center – Neurosciences and cancer, Inserm U1172/Université de Lille/Lille University Hospital), is challenging the hypothesis according to which PCOS only alters the ovaries, by showing that it also modifies the activities of brain neurons in the hypothalamus, which are responsible for controlling reproduction. Implicated is a hormone produced by the ovaries and involved in their functioning: anti-Müllerian hormone (AMH). Patients with PCOS present blood levels of this hormone which are two to three times higher, and directly linked to the severity of the disease.

The team based its research on two observations made in pregnant women with PCOS. The first is its already-known correlation with hyperandrogenism (excessive production of androgens). The second, a new observation, is its correlation with a heightened production of AMH during pregnancy. The researchers have shown that mice treated with AMH during gestation give birth to females that develop the symptoms characteristic of PCOS in adulthood. The production of abnormally high levels of AMH during the prenatal period could therefore be responsible for gestational hyperandrogenism and the abnormal hormonal impregnation of the fetus.

The team also observed that, in mice mimicking PCOS, *in utero* exposure to abnormally high levels of AMH was responsible for increased activity of the GnRH protein-secreting hypothalamic neurons in adulthood. This intense GnRH production stimulates the heightened production of another hormone, luteinizing hormone (LH), which itself stimulates the production of androgens. Paolo Giacobini and his coworkers, including Brooke Tata and Nour El Houda Mimouni, joint first authors of the article, demonstrate here that prenatal

exposure to AMH triggers a genuine chain reaction in offspring: the hypothalamic neurons start secreting more GnRH, which increases LH production by the pituitary gland, in the end triggering this characteristic increase of androgens in the ovaries, which is responsible for the disrupted ovulation observed in PCOS.

Armed with these findings, the researchers applied to mice mimicking PCOS a specific treatment that “normalizes” the increased action of GnRH on LH production, thereby restoring their fertility. These findings observed in the mouse model offer unheard of therapeutic perspectives which remain to be confirmed at human level.

Sources

Elevated prenatal anti-Müllerian hormone reprograms the fetus and induces polycystic ovary syndrome in adulthood

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