Neural mechanism facilitates network integration for fertility-controlling neurons and sexual maturation

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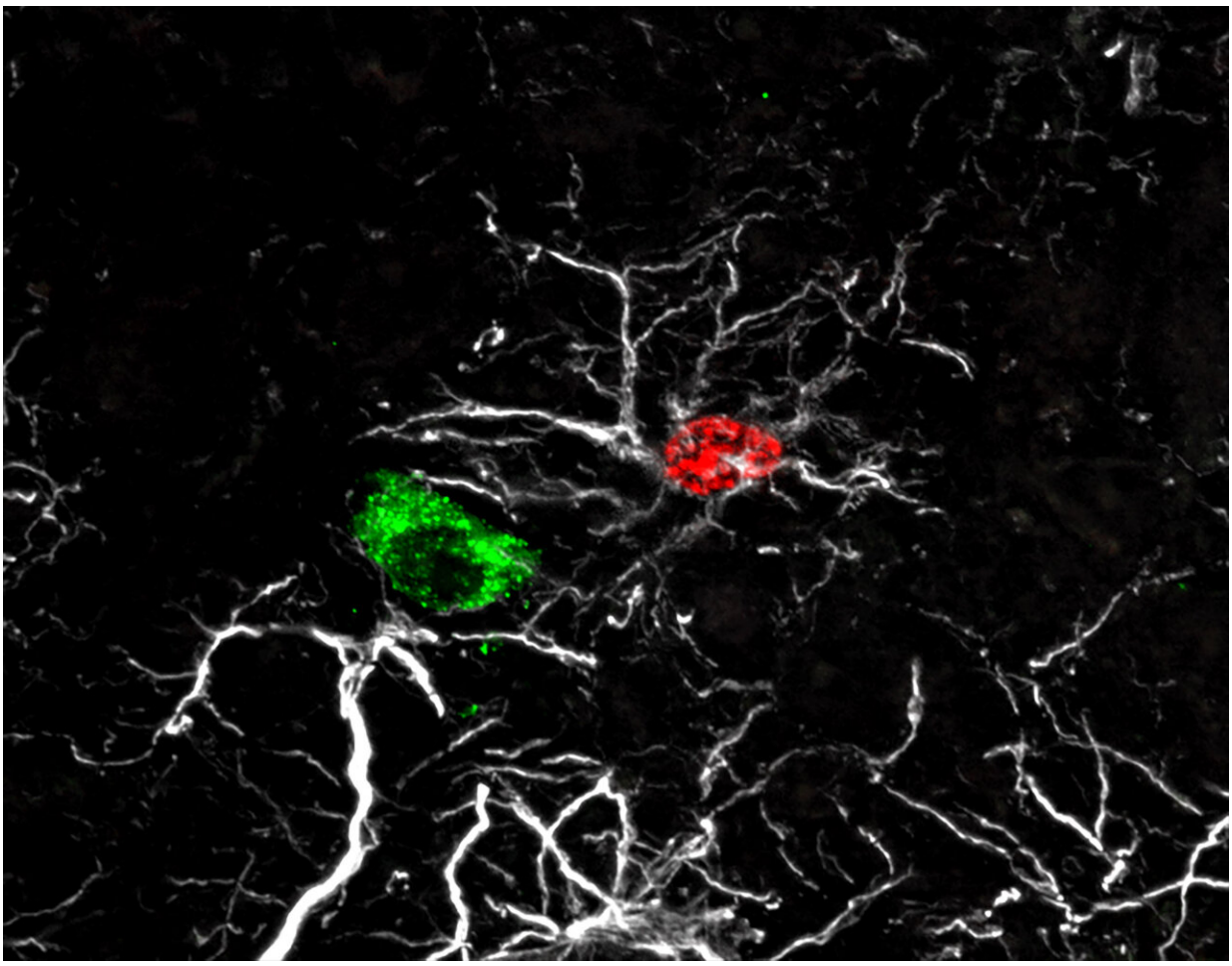

Credit: Pellegrino et al.

Gonadotropin-releasing hormone (GnRH) is the primary hormone regulating sexual reproduction in humans and other mammals. Past neuroscience studies have found that GnRH-producing neurons migrate from a region in the nose known as the nasal placode to the anterior part of the brain (i.e., the forebrain) before humans and other mammals are born.

The function of these neurons, however, is established post-birth, during infancy. In the initial stages of postnatal development, in fact, GnRH-producing neurons are integrated within a complex neuroglial network, which ultimately defines their physiological function.

Researchers at University of Lille and other institutes across Europe have recently carried out a study aimed at investigating the neural mechanisms through which these important neurons are integrated into complex networks during infancy. Their paper, published in *Nature Neuroscience*, unveils a previously unknown neural pathway through which the brain of humans and other mammals could control the process of sexual maturation.

"This study emerged when I was a postdoctoral researcher in the laboratory of Sergio R Ojeda at the Oregon National Primate Research Centre (Beaverton, OR, U.S.) twenty years ago (1999–2002)," Vincent Prevot, one of the researchers who carried out the study, told Medical Xpress. "At the time, astrocytes were just emerging as being key partners in neuronal information processing, a concept that had been established by Dr. Ojeda a decade before."

In a previous study, Prevot and some of his colleagues used state-of-the-art transgenic approaches to investigate astrocyte-to-GnRH-neuron communication processes. Their findings, published in 2003, showed that these processes play a crucial role in the sexual maturation of female mice.

"The obvious next question was to determine how the glial entourage of the GnRH neurons was established in the hypothalamus during postnatal development, as neurons are known to be born during embryonic development, but astrogenesis (i.e., the birth of astrocytes) has been found to occur in other brain areas during the last days of gestation and in the first weeks after birth," Ariane Sharif, who co-directed the study with Prevot, told Medical Xpress.

In their initial experiments, Prevot and Sharif used BrdU, an analog of the thymidine getting integrated in the DNA of newly born cells when a mother cell is copying its genetic material to transmit it to its daughter cells. When they injected this analog into rat pups, they found that astrocytes formed in the hypothalamus (i.e., the area of the brain that produces hormones) during the newborns' first two weeks of life.

The researchers observed that these newly formed astrocytes were preferentially associated to GnRH neurons. Interestingly, they also found that GnRH neurons appeared to attract newly born astrocytes in their vicinity.

"The birth of cells was observed by killing the animals two hours after BrdU injection and the attraction of newly differentiated astrocytes was seen by killing the animals seven days after a single BrdU injection," Prevot explained. "While the number of GnRH neurons do not change during postnatal life, a much greater proportion of GnRH neurons were found to be associated to newborn cells at 7d than at 2h post-BrdU injection."

Prevot and Sharif were surprised to find that only astrocytes born at the beginning of the pups' second week of life escorted GnRH neurons into adulthood by morphologically associating with them. To investigate this finding further and better understand its implications, the team had to identify a strategy to inhibit the birth of new cells in the vicinity of

GnRH neurons so that they could assess the effect of astrocyte production on postnatal sexual maturation.

"This was not as easy task, as the infantile brain is constantly growing and thus the local chronic delivery of antimitotic drugs in the neighborhood of GnRH neurons is a hard goal to reach," Sharif said. "Thanks to the collaboration with pharmaceutical scientists, we designed microparticles that could be implanted in the hypothalamus of the infantile rats and release antimitotic drugs for 1 week only."

The microparticles designed by Prevot, Sharif and their colleagues could prevent the formation of new astrocytes in the vicinity of GnRH neurons. By administering them to the mice pups, therefore, they could assess the impact of astrocyte production during infancy on sexual maturation. The results of these experiments yielded very interesting results, as the team found that the administration of the microparticles had striking consequences on the fertility and sexual maturation of female rats.

"Intriguingly, the phenotype resulting from the inhibition of the ability of GnRH neurons to recruit astrocytes resembled the one described by a Belgian researcher with whom I was transitioning in Dr. Ojeda's lab, Prof. Anne Simone-Parent at Liège University Hospital," Prevot said. "Prof. Simone-Parent has been specifically investigating the effects of endocrine disruptors in female rats during postnatal development."

In their following tests, Prevot, Sharif and their colleagues found that treating female pups with very low doses of bisphenol A (i.e., a synthetic organic compound often used to manufacture polymers) impacted the GnRH neurons' ability to recruit astrocytes, naturally reproducing the genetic effects of antimitotic drugs. Antimitotic drugs are pharmaceutical products used to treat cancer that block tumor growth by killing cells that are entering division (i.e., mitosis).

"We then used additional state-of-the-art approaches to identify how GnRH neurons could communicate with newborn cells and why the glial escort was important to the GnRH neuron," Prevot said. "Concerning the latter point, using fluorescent labeling to visualize proteins and electrophysiology (i.e., monitoring the electrical activity of the GnRH neurons) we could identify that it was key for the integration of the GnRH neuron in the neuronal network they use to adapt reproductive function to body homeostasis and environmental constrains."

The recent study carried out by this team of researchers could have important implications for future research, as it clearly shows that GnRH-producing neurons create their own glial environment during the first stages of postnatal development. It also highlights how impairing their ability to do this, for instance by injecting substances that disrupt their natural processes, can impact postnatal development, with potentially severe and long-lasting health consequences.

"We now plan to conduct further studies aimed at identifying the exact mechanisms by which endocrine disruptors act on glial cells to prevent their docking onto (associating morphologically and functionally with) neurons that need them," Sharif and Prevot added.

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