Revealing the Intricate Links Between Metabolism and Reproduction

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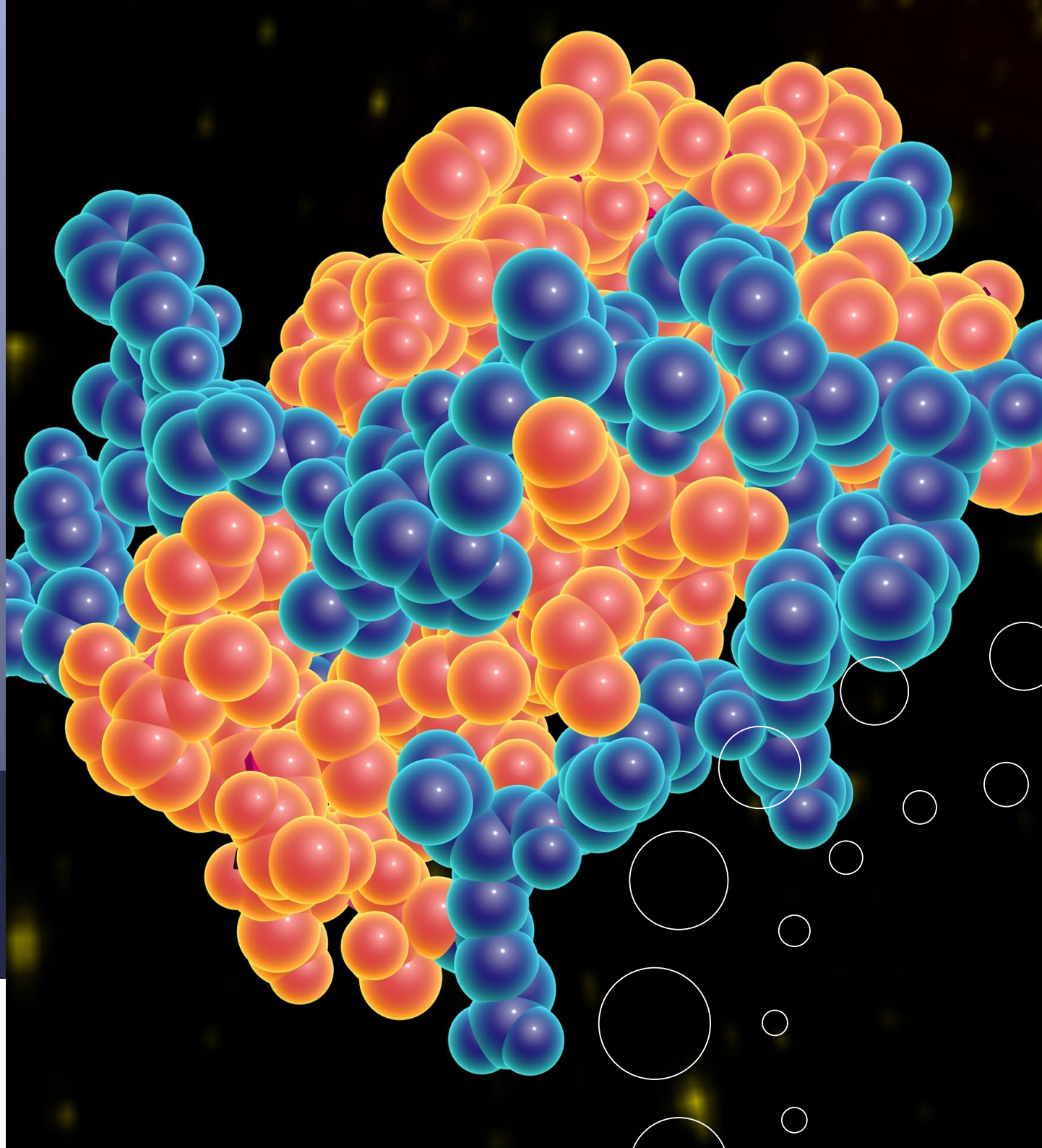
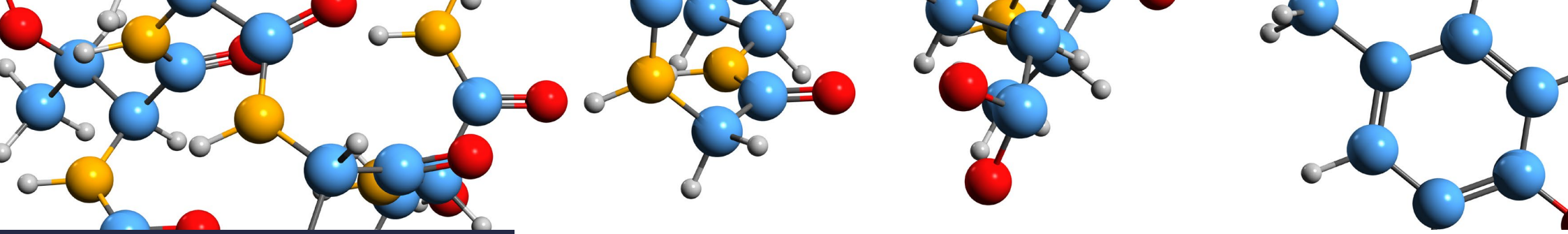




Revealing the Intricate Links Between Metabolism and Reproduction

The brain plays a vital role in controlling reproductive functions. It helps to maintain a delicate balance of hormones, all of which can be affected by the metabolism. Investigating the impact of the metabolism on reproductive development and function is critical to a better understanding of health and diseases. Professor Carol Fuzeti Elias and Dr Cristina Sáenz de Miera Patín from the University of Michigan in the USA, carry out groundbreaking research in neuroscience, exploring the molecular and neural mechanisms at play.

Nutrition Versus Reproduction

Nutrition and reproduction are closely linked. The process of reproduction has a high energy demand and, as such, can be significantly affected by the nutritional status of the individual. When nutrition is poor (for example, due to the scarcity of food), fertility is suppressed, conserving energy for critical functions. On the flip side, excess fatty tissues in the body can negatively affect ovulation, increase the risks of pregnancy complications, and kick-start puberty at a younger age. This metabolic aspect of reproductive function is coordinated by communications between a part of the brain called the hypothalamus, the pituitary gland, and the gonads, which are the ovaries in females and testes in males. This communication loop is called the hypothalamo–pituitary–gonadal (HPG) axis.

Dr Cristina Sáenz de Miera is based in the Department of Molecular and Integrative Physiology along with Dr Carol Elias, who also works in the Department of Obstetrics and Gynecology at the University of Michigan. They explain that the sites of action and mechanisms involved in the nutritional regulation of the HPG axis are not fully understood. Their research aims to determine the neural and molecular mechanisms by which metabolic imbalances can disrupt reproductive physiology.

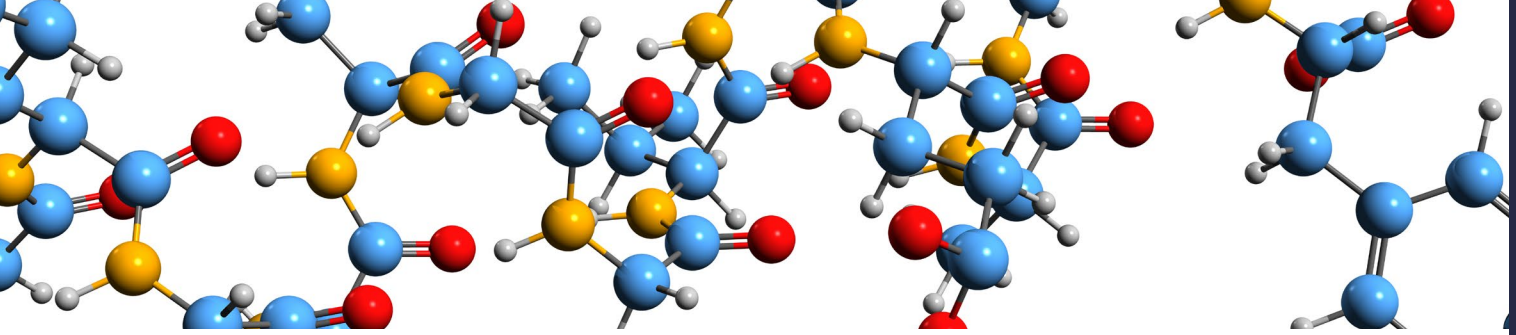
Essential Metabolic Hormone: Leptin

Dr Elias and Dr Sáenz de Miera use genetically modified mouse models and molecular biology tools to carry out their important research. They highlight the crucial metabolic signalling hormone called leptin, which acts on the brain to regulate reproductive processes. Both mice and humans with problems producing leptin (or the receptor on the cells that it communicates with) are infertile and do not go through puberty. Previous research with genetically modified mice lacking the leptin receptor (Lepr) gene showed that they, in fact, regained their fertility when this gene was restored in their neurons.

The team adds that leptin certainly impacts the HPG axis indirectly. They explain that certain types of neurons, critical for reproduction, called gonadotropin-releasing hormone or GnRH neurons, do not feature Lepr. However, they do receive communications directly from neurons that do, highlighting that the exact neural circuitry is not currently known. The enigma continues to grow when looking more closely at the hypothalamus with its specialised features and functions.

Mysteries of the Ventral Premammillary Nucleus

The colleagues explain that the ventral premammillary nucleus (PMv) is a part of the hypothalamus that has often been overlooked in research. It is a glutamatergic nucleus, releasing the vital neurotransmitter (a molecule used for communication between neurons) called glutamate. Additionally, it is rich in neurons which feature LepR. Studies in rats with lesions on the PMv show disrupted hormone (oestrous) cycles and a reduced ability of leptin to boost reproductive hormones, such as the luteinising hormone. They also highlight that restoring LepR, specifically in the PMv of a mouse that has no LepR, rescues fertility and puberty. Neurons responsive to leptin in the PMv also make contact with neurons important to the regulation of the reproductive function, e.g., the GnRH neurons, among others. However, with the complex nature of the interactions of these hormones, neurotransmitters, and receptors, various inconsistencies have become apparent over the years of research.



> Both mice and humans with problems producing leptin (or the receptor on the cells that it communicates with) are infertile and do not go through puberty.

Dr Elias and Dr Sáenz de Miera are attempting to unravel the mysteries of this system. In a recent publication, they aimed to determine the role of glutamate signalling from leptin-responsive PMv neurons on puberty and fertility.

Chemogenetics and DREADDS

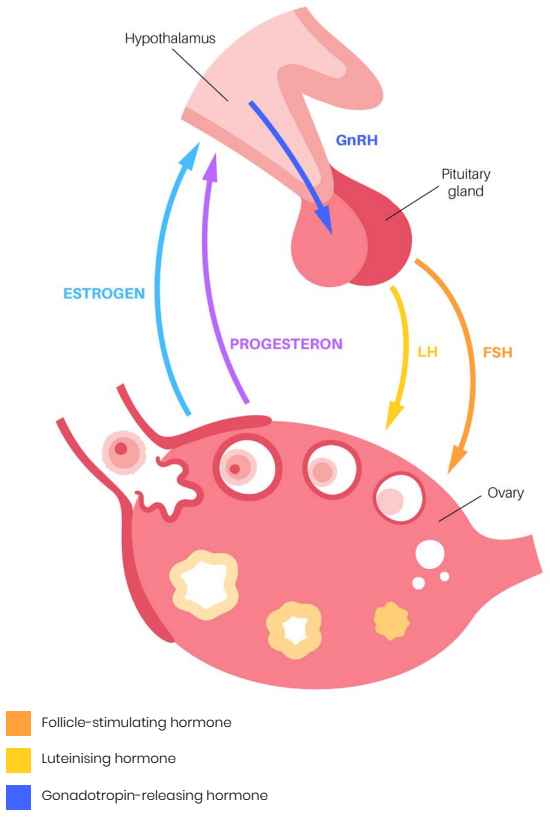
Chemogenetics involves using molecules which have been engineered to activate or inhibit neurons. For the first part of their recent study, they used chemogenetics to work out if stimulation of PMv neurons induced the release of luteinising hormone in adult female mice during the dioestrous part of their cycle. This is the quiet period between the ovulatory days when the mice have low reproductive hormones.

They used the chemogenetic system 'designer receptor exclusively activated by designer drugs' – DREADDs – in genetically altered mice. This is a type of artificially engineered receptor that is only activated by particular substances, which can then be used to investigate the activity of neurons. Mice expressing the DREADDs receptor in the PMv Lepr neurons were treated with the activating drug, and blood samples were taken from the mice before and for one hour after the drug administration to determine hormone level changes. The colleagues reported increased luteinising hormone levels due to the activation of PMv neurons, plus levels were correlated to the number of neurons activated in the PMv.

Puberty, the Brain, and Beyond

Dr Elias and Dr Sáenz de Miera next used the genetically altered, or transgenic mice, to determine if lack of glutamate neurotransmission in Lepr neurons negatively affects puberty and normal reproductive functions. By removing proteins responsible for transporting glutamate to the nerve terminals, specifically in neurons that have Lepr, they found that the mice showed a delay in puberty, disruption to their oestrous cycle and luteinising hormone secretion, and an accumulation of gonadotropin-releasing hormone in the brain. These findings suggested that the mice that do not secrete glutamate in Lepr neurons have a defect in the release of GnRH, leading to deficits in reproductive function.

The team proceeded to deduce if the neurotransmitter glutamate is required for the actions of leptin in the PMv that lead to pubertal development. They used another set of genetically modified mouse models with a global lack of Lepr and deletion of glutamate transporters, specifically in PMv neurons. As they showed before, they found that restoration of Lepr in PMv neurons of obese and infertile mice restores puberty and fertility in the mice with intact glutamate neurotransmission. However, when these mice's PMv neurons had deficient glutamate neurotransmission (due to the specific deletion of glutamate transporters) – they saw no signs of puberty or rescued fertility. The team reported that their overall findings indicate that glutamate neurotransmission from LepR neurons in the PMV is necessary for leptin action in puberty and fertility. Their findings, which are supported by high-quality, solid data, will be of great significance for research on obesity and diabetes and their deleterious effects on fertility and pregnancy.



Article written by Luisa Postlethwaite, MPharm.

MEET THE RESEARCHERS

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Professor Carol Fuzeti Elias completed her MS in Neuroanatomy and her PhD in Neuroscience and Behaviour at the University of São Paulo, Brazil. She underwent postdoctoral training in Neurology and Neuroendocrinology at Harvard Medical School's Beth Israel Deaconess Medical Centre in the USA. Over her well-published career, she has held positions in the Institute of Biomedical Sciences at the University of São Paulo, and the Division of Hypothalamic Research at UT Southwestern Medical Centre in Dallas, USA. She is currently a professor in the Department of Molecular and Integrative Physiology, and the Department of Obstetrics and Gynecology, at the University of Michigan in the USA. She is also the Director of the Mouse Metabolic Phenotyping Center and the Neuroscience Graduate Program. In 2020, she was elected a fellow of the American Academy for the Advancement of Sciences and is a member of the Latin American Academy of Sciences. Her main research interests are in neuroendocrinology, metabolism, and reproductive physiology.

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Dr Cristina Sáenz de Miera Patín obtained her BSc in Biology at the Autonomous University of Madrid in Spain. She also completed an Erasmus Exchange Program with the University of Manchester, UK. In 2014, she obtained her joint PhD in Integrative Physiology-Neurosciences from the University of Strasbourg, France, and the University of Aberdeen, UK. She underwent postgraduate training in the Institute of Cellular and Integrative Neuroscience at the University of Strasbourg, the Department of Molecular, Cellular and Developmental Biology and also the Department of Molecular and Integrative Physiology at the University of Michigan, where she holds her current position of Research Investigator. In 2024, she received the Bishr Omary Physiology Research Investigator Award from the University of Michigan. She is a member of the American Physiological Society and the Panamerican Neuroendocrine Society. Her research interests are in the development and environmental regulation of neuroendocrine systems, and the central control of metabolism and reproduction.

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FURTHER READING

C Sáenz de Miera, N Bellefontaine, SJ Allen, *et al*., Glutamate neurotransmission from leptin receptor cells is required for typical puberty and reproductive function in female mice, *eLife*, 2024, 13:RP93204, DOI: https://doi.org/10.7554/eLife.93204