Insights on metabolic health and reproductive wellness with Dr. Carol Elias

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In this exclusive interview, Dr. Carol Elias simplifies the complex link between metabolism and reproduction, sharing insights into the science behind our physiological balance

Could you tell us a bit about what sparked your initial interest in researching the connection between metabolism and reproductive health?

During my college years, I developed a fascination for the brain and all neuroscience research. I decided to follow an academic path and sought a graduate program that would provide me with an opportunity to work in this field. In the final years of my PhD in Neuroscience and Behavior at the University of São Paulo, Brazil, the discovery of leptin, a hormone that signals energy stored as fat, had a profound impact on the field of endocrinology. This breakthrough garnered specific attention in the realm of neuroendocrinology, as the brain is leptin's primary target.

My research contributed to the early findings identifying the brain sites and circuitry associated with leptin responses. During these studies at Harvard Medical School, USA, I was intrigued by the fact that several brain sites tied to reproductive control demonstrated dense expression of leptin receptors. Given that loss-of- function mutations in either leptin or leptin receptors cause obesity, diabetes, and reproductive deficits, the interconnection between metabolism and reproductive health emerged as the principal focus of my research.

Your research explores fascinating and complex interactions between the brain, hormones, and our health. Can you share a favourite or surprising finding from your work that highlights the interconnectedness of these systems?

Reproductive health is critically important for the survival of any species. We typically expect that if a genetic mutation leads to deleterious consequences for reproductive capacity, the mutation will not persist in the species' genome. This is because such individuals would be unable to pass the defective gene to subsequent generations.

However, a disruption of a gene that promotes the accumulation of energy reserves enhances survival in conditions of limited energy availability – a common scenario throughout thousands of years of human existence. With industrialization and increased access to food, both in developed and developing countries, this situation has changed.

Overweight and obesity rates have risen considerably, introducing new health challenges. Interestingly, an accumulation of energy as fat causes obesity, diabetes and also reproductive deficits."

Our work made an intriguing discovery: we identified brain areas that respond to leptin and control reproduction, independent of metabolism. We found that a specific population of neurons plays a key role in leptin's action on reproductive function yet exhibits virtually no role in metabolic regulation. The sex differences we found were also striking. While specific brain areas are crucial for the metabolic control of reproduction in females, their role in male reproduction remains debatable.

In your lab, you investigate how metabolic imbalances disrupt the neuroendocrine system. Can you explain the key pathways or mechanisms involved in this disruption, especially during critical developmental stages like puberty?

Different circulating hormones signal an individual's energy store and nutritional state. These hormones bind to receptors expressed in neurons located in distinct areas, or nuclei, of the hypothalamus. These neurons sense metabolic signals such as leptin, ghrelin, and insulin and convey the information to brain areas that control hunger, energy expenditure, temperature, and other functions, including reproduction.

If there is too little energy, the brain receives this information and regulates our physiology by reducing energy expenditure, increasing hunger, and inhibiting reproductive function. Conversely, if too much energy is stored, as is the case with overweight and obesity, the neurons develop resistance to the hormones and cease responding.

During pubertal development, many brain areas are still developing, and the circulating hormones have the ability to shape this development. If an imbalance is in place, it may create conditions that increase susceptibility to the development of metabolic diseases such as type 2 diabetes, cardiometabolic dysfunction, and fat liver disease.

How do metabolic imbalances affect the neuroendocrine systems of males and females differently, and what are the potential health consequences for each?

How metabolic imbalances impact neuroendocrine systems in both sexes is not yet completely understood.

Regrettably, many early studies failed to address both sexes, leaving our understanding incomplete. Excess stored energy, as in obesity, adversely affects neuroendocrine function and fertility in both sexes, though the specifics can differ.

For example, increased adiposity can exacerbate ovulatory dysfunctions and polycystic ovary syndrome and could potentially reduce reproductive capacity by altering the neuroendocrine axis functioning in women. Among obese men, fertility tends to be

reduced primarily due to defective gonadal steroidogenesis, as well as compromised sperm motility and quality.

Childhood obesity is a growing concern globally. Can you elaborate on the specific risks early-onset obesity poses to long-term reproductive health and the underlying hormonal changes involved?

Research has highlighted the connection between childhood obesity and the rising rates of early puberty in girls, with potential implications for boys as well. Early menarche in girls is linked to an elevated risk of adult obesity, type 2 diabetes, and endocrine cancers. It is also associated with higher rates of psychosocial and mental health issues, including depression.

Your lab utilizes advanced techniques like genetically modified mice and brain mapping tools. Can you share how these methods help you dissect the intricate networks governing the link between metabolism and reproduction?

The use of genetic tools and mouse models has brought incredible development to the field. Rodents possess similar physiology to humans and respond to nutrition in ways that mirror human responses within the sphere of neuroendocrine regulation. Many genetic mutations cause similar deficits in both rodents and humans.

We leverage these similarities to identify critical genes and produce mutations in mice that mimic human diseases. Studying the genetic mutations in mice helps us understand the roles of these genes and how to improve health in the event of diseases.

Looking ahead, what are the most exciting frontiers in your research field, and what new questions are you hoping to tackle in the coming years?

There is still much to learn in this field. Our laboratory is currently exploring the role of sex hormones in metabolic regulation, particularly androgens. Androgen receptors are widespread in the brains of both males and females, but their role in neuroendocrine regulation and metabolism is not well known. We are also interested in investigating whether childhood obesity alters brain development and the mechanisms by which it may shape the neuroendocrine responses in adult life.

Beyond the scientific implications, can you discuss the broader societal impact of your research? How can increased awareness of the metabolic-reproductive link benefit public health education and individual health choices?

As I mentioned above, childhood obesity may be the root of many metabolic diseases in adulthood. If associated with early puberty, the deleterious health consequences may be exacerbated with the development of cardiovascular diseases, type 2 diabetes, and increased risk of endocrine cancers. Obesity is one of the most common metabolic dysfunctions highly prevalent in adults of reproductive age. In the United States,

according to 2017–2018 National Health and Nutrition Examination Survey (NHANES, USA), about 30% of the population is overweight, and 40% have obesity. These numbers are similar in Europe. The 2022 publication from the World Health Organization claims that 59% of the European population is overweight or obese.

As I mentioned, obesity, in most cases, is associated with reproductive deficits. Elevated adiposity aggravates polycystic ovary syndrome and ovulatory dysfunctions and may induce subfertility or infertility in men and women. However, a high percentage of women with obesity can conceive, being thereby exposed to increased risks of pregnancy complications and maternal or fetal morbidity and mortality. Women with obesity have a higher risk of early and recurrent miscarriages and double the risk of preterm birth, stillbirth and neonatal death compared to age-matched non-obese counterparts. Congenital abnormalities, including neural tube and cardiac defects, orofacial malformations, and intestinal anomalies (e.g., anorectal atresia and omphalocele), are also more common in children of women with obesity during gestation.

The exact cause(s) behind these deleterious effects are incompletely understood. It is believed that high adiposity may favor the installation of an adverse intrauterine milieu or placental insufficiency, impairing blood flow and nutrient exchange. Public awareness is fundamental to reducing obesity-induced economic burden and deleterious health consequences for future generations.

Are there any misconceptions or myths surrounding the connection between metabolism and reproductive health that you encounter frequently? How do you approach correcting those misconceptions and making your research accessible to a broader audience?

Specifically, in relation to our research, misconceptions are often tied to the health effects of obesity and its association with adverse reproductive outcomes. In some instances, obesity is not viewed as a health concern, but rather an aesthetic issue, with people having differing preferences regarding body shape. However, this is unquestionably a misconception, one that I strive to clarify by referencing research findings and underlining the potential severe health risks caused by obesity.

Similarly, the interplay between metabolism and reproduction is routinely overlooked, especially in the context of women of reproductive age with obesity who are attempting to conceive. This can be a sensitive topic to discuss, but it is crucial for the well-being of both women and their children.

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