

Scientists discover how our brain uses nutritional state to regulate growth and age at puberty

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Scientists have discovered how a receptor in the brain, called MC3R, detects the nutritional state of the body and regulates the timing of

puberty and rate of growth in children and increases in lean muscle mass.

These findings, published today in the journal [*Nature*](#), may explain how humans have been growing taller and reaching sexual maturity earlier over the past century. Over the 20th century, [average height increased by](#) about 10 cm in the UK, and up to 20 cm in other countries.

While scientists have long suggested that this phenomenon could be related to more reliable access to food for [pregnant women](#) and children, until now, precisely how the body senses its state of nutrition and turns that information into growth and sexual maturation had not been understood.

It was already known that signals reach the brain to indicate the body's nutritional state, such as the hormones leptin, produced in adipose (fat) cells, and insulin, produced in response to increases in blood sugar levels. In a part of the brain called the hypothalamus, these hormones act on a small group of neurons that produce signals called melanocortins.

The melanocortins act on a variety of receptors, two of which are present in the brain. One of these, the melanocortin 4 receptor (MC4R) has previously been shown to regulate appetite and lack of MC4R results in obesity; however, the MC4R system does not control the effect of nutrition on growth and timing of puberty.

Now, a study, led by researchers from the MRC Metabolic Diseases Unit and the MRC Epidemiology Unit (both part of the Wellcome-MRC Institute of Metabolic Science) at the University of Cambridge, with collaborators from Queen Mary University of London, University of Bristol, University of Michigan and Vanderbilt University, has discovered a role for the brain's other melanocortin receptor, which is known as the melanocortin 3 receptor (MC3R).

They found that in response to nutritional signals the MC3R system controls the release of key hormones regulating growth and sexual maturation.

To show the link in humans, the scientists searched amongst the half a million volunteers in UK Biobank for people with naturally occurring [genetic mutations](#) that disrupt the function of the MC3R. They identified a few thousand people who carried various [mutations](#) in the gene for MC3R and found these people were on average shorter and went into puberty later than those with no mutation.

For example, they identified 812 women who had the same mutation in one of their two copies of the MC3R gene. This mutation only partly reduced the ability of the receptor to work. Despite this subtle effect, women who carried this were on average 4.7 months older at puberty than those without the mutation.

People with mutations that reduced the function of MC3R were also shorter and had lower amounts of lean tissue, such as muscle, but it had no influence on how much fat they carried.

To confirm these findings in children, they studied almost 6,000 participants from the Avon Longitudinal Study of Parents and Children (ALSPAC) and identified six children with mutations in MC3R. The six children were shorter and had lower lean mass and weight throughout childhood, showing that this effect starts very early in life.

All the people identified in these studies had a mutation in only one of the two copies of the gene. Finding mutations in both copies of the gene is vanishingly rare, but in another cohort the researchers were able to identify an individual in the [Genes and Health study](#) with a very damaging mutation in both copies of the gene. This person was very short and went into puberty after the age of 20.

This same phenomenon linking adequate nutritional body stores to reproductive maturity is seen right across the [animal kingdom](#), so the researchers conducted studies in mice to confirm that the MC3R pathway operates across species. Work in the laboratory of Dr. Roger Cone at the University of Michigan, who had previously demonstrated a role for the MC3R in the control of growth and lean mass in mice, showed that while normal mice shut off their reproductive cycle when they underwent a period of food deprivation, mice engineered to lack the MC3R did not. This confirmed that MC3R is a necessary part of how the nutritional state controls sex hormone production.

Professor Sir Stephen O'Rahilly, a senior author on the study and Director of the MRC Metabolic Diseases Unit at the University of Cambridge, said: "This discovery shows how the brain can sense nutrients and interpret this to make subconscious decisions that influence our growth and sexual development. Identifying the pathway in the brain whereby nutrition turns into growth and puberty explains a global phenomenon of increasing height and decreasing age at puberty that has puzzled scientists for a century.

"Our findings have immediate practical implications for the testing of children with serious delays in growth and pubertal development for mutations in the MC3R.

"This research may have wider implications beyond child development and reproductive health. Many chronic diseases are associated with the loss of lean mass, including muscle, with resultant frailty. This responds poorly to simple nutritional supplements such as protein-rich drinks. The finding that the activity of the MC3R pathway influences the amount of lean mass carried by a person suggests that future research should investigate if drugs that selectively activate the MC3R might help redirect calories into muscle and other lean tissues with the prospect of improving the physical functional of such patients."

Professor John Perry, a senior author on the study from the MRC Epidemiology Unit at the University of Cambridge, said: "This is such an exciting time for human genetics. By analyzing the genetic sequences of large numbers of research participants, we can now understand fundamental biological processes that have remained elusive until now. By combining these studies with experiments in cellular and animal models, we will continue to uncover new insights and understand the mechanisms behind human growth and metabolic disease."

More information: Stephen O'Rahilly, MC3R links nutritional state to childhood growth and the timing of puberty, *Nature* (2021). [DOI: 10.1038/s41586-021-04088-9](https://doi.org/10.1038/s41586-021-04088-9).
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