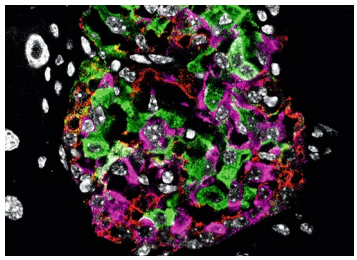
There are amendments to 10.1038/s41574-020-0350-z

DIABETES

Restoring β-cells



The image shows a pancreatic islet from a mouse with streptozotocin-induced diabetes mellitus, with staining for the most frequent cell types in these islets. White stains for the cell nucleus (DAPI staining). β-cells (insulin) are stained green, α-cells (glucagon) are red and δ-cells (somatostatin) are in magenta. Image courtesy of Heiko Lickert, Institute for Diabetes and Regeneration at the Helmholtz Center Munich, Germany.

Dedifferentiation of β-cells is thought to be a major mechanism underlying β-cell loss and dysfunction in type 1 and type 2 diabetes mellitus; however, whether this process could be targeted pharmacologically was unknown. New research demonstrates that β-cell dedifferentiation can be targeted to restore β-cell function in mice with streptozotocin-induced diabetes mellitus.

Previous papers have shown that a GLP1–oestrogen conjugate can reverse the metabolic syndrome in mice and that oestrogen has positive effects on β-cells. "Hence, in our current study we hypothesized that the targeted delivery of oestrogen to GLP1R-expressing pancreatic β-cells could achieve additional metabolic benefits to stop or revert diabetes mellitus progression," explain authors Stephan Sachs and Heiko Lickert. The authors treated mice with multiple low doses of streptozotocin to induce diabetes mellitus while allowing some β-cells to survive. The mice were then divided into treatment groups to receive: a GLP1–oestrogen conjugate; GLP1; oestrogen; a long-acting pegylated insulin analogue (PEG-insulin); or a combination of GLP1–oestrogen and PEG-insulin. "Using single-cell RNA sequencing (scRNA-seq), we show that the surviving β-cells after the initial streptozotocin treatment dedifferentiate into a dysfunctional state," explain Sachs and Lickert. This data also allowed the researchers to compile a detailed transcriptomic landscape of dedifferentiated β-cells.

The scRNA-seq data also demonstrated that the PEG-insulin treatment and combined treatment of GLP1–oestrogen and PEG-insulin led to redifferentiation of β-cells. Furthermore, this redifferentiation resulted in functional β-cell recovery and remission of diabetes mellitus in the mouse model. "Combining GLP1–oestrogen with PEG-insulin therapy achieved superior metabolic benefits compared with the mono-treatments, normalizing glycaemia and glucose tolerance, increasing pancreatic insulin content and increasing the number of β-cells," say Sachs and Lickert. The combination therapy also meant that the dose of insulin could be reduced, mitigating the adverse effects of insulin treatment. "We could also show that GLP1–oestrogen, but not GLP1 or oestrogen alone, increases human β-cell function when human pancreatic islets are exposed to cytokine stress, which is known to impair human β-cell function," explain Sachs and Lickert. The researchers hope that their work will pave the way for future studies in this area and ultimately the development of novel therapies to regenerate β-cells and result in diabetes mellitus remission.

Claire Greenhill

ORIGINAL ARTICLE Sachs, S. et al. Targeted pharmacological therapy restores β-cell function for diabetes remission. *Nat. Metab.* **2**, 192–209 (2020)

NUTRITION

Metabolic effects of sucralose

The effects of consuming low-calorie sweeteners such as sucralose are widely debated, with the literature containing conflicting studies. A new paper suggests that when sucralose is consumed with carbohydrates, insulin sensitivity is impaired in healthy humans.

The researchers randomly assigned 45 healthy volunteers to consume beverages sweetened with sucralose, beverages sweetened with sucrose or beverages containing maltodextrin (a carbohydrate) and sweetened with sucralose. The participants were non-regular consumers of low-calorie sweeteners and consumed seven portions of their assigned beverage over 2 weeks.

All the participants underwent an oral glucose tolerance test and blood tests at baseline and after the 2-week exposure. These tests revealed that consuming sucralose with carbohydrate, but not without the carbohydrate, resulted in reduced insulin sensitivity. The participants also underwent fMRI, which showed that the participants who consumed sucralose with maltodextrin had reduced responses to sweet taste (but not sour, salty or savoury tastes) in the midbrain, insular and cingulate areas of the brain. These changes were not seen in the other groups of participants. A follow-up experiment in which participants consumed a beverage containing just maltodextrin found no evidence of altered insulin sensitivity, suggesting that it is the combination of sucralose and carbohydrate that is driving the changes observed in this study.

The authors conclude that their results suggest consuming low-calorie sweeteners with carbohydrate causes metabolic dysfunction and

PARATHYROID GLAND

Insights into parathyroid hormone secretion

Owing to a lack of suitable models, the molecular mechanisms of parathyroid hormone (PTH) hypersecretion in hyperparathyroidism (HPT) are unclear. A study published in *Nature Metabolism* now sheds light on these mechanisms.

In the parathyroid gland (PTG), the calcium-sensing receptor (CaSR) senses elevated Ca^{2+} and forms homomeric complexes to negatively feedback and regulate PTH levels, a pathway that is commonly disrupted in HPT. It is unclear, however, how HPT arises in hypocalcaemia or when CaSR expression is abnormal.

"We overcame the previous technical limitations by generating mice with single and compound PTG-specific gene knockouts and by developing a high-fidelity ex vivo PTG culture system," explain corresponding authors Wenhan Chang and Jean-Pierre Vilardaga. Previous work by their group showed that CaSR forms heteromeric complexes with γ-aminobutyric acid B_1 receptor ($GABA_{B1}R$) in cell culture, so the researchers generated PTG-specific knockout mouse models, enabling them to determine cell-autonomous effects of CaSR, $GABA_{B1}R$ and GAD1/2, which

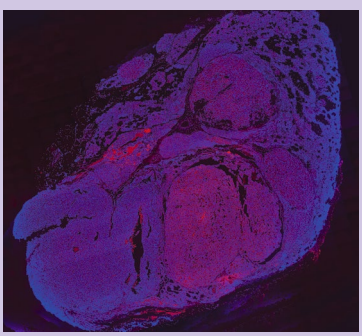


Image reprinted courtesy of Wenhan Chang/University of California. Increased CaSR–$GABA_{B1}R$ heterodimerization (red) in hyperplastic portion of PTGs (blue) from patients with secondary HPT.

Credit: Peter Dazeley/Getty

reduced central sensitivity to sweet taste. The researchers suggest that the consumption of low-calorie sweeteners in combination with carbohydrates could therefore have a negative effect on metabolic health. However, they note that more research is needed as their study had a small sample size, a short period of exposure and no washout period to assess the reversibility of the changes.

Claire Greenhill

> A new paper suggests that when sucralose is consumed with carbohydrates, insulin sensitivity is impaired in healthy humans

ORIGINAL ARTICLE Dalenberg, J. R. et al. Short-term consumption of sucralose with, but not without, carbohydrate impairs neural and metabolic sensitivity to sugar in humans. *Cell Metab.* **31**, 493–502 (2020)

> CaSR forms heteromeric complexes with γ-aminobutyric acid B_1 receptor

is the rate limiting enzyme for GABA synthesis.

"Key and unexpected findings included an increased formation of CaSR–$GABA_{B1}$R heteromers in hyperparathyroid states, as well as PTH hypersecretion due to the negative allosteric action of $GABA_{B1}$R on CaSR signalling via heterotrimeric G proteins," describe Chang and Vilardaga. "In addition, we saw synthesis of GABA in PTGs, which might act via an autocrine pathway where the release of GABA binds directly to $GABA_{B1}$R–CaSR heteromers, thus promoting the PTH hypersecretion encountered in HPT."

The present study describes new molecular mechanisms for PTH hypersecretion in HPT. These findings could have implications for physiological processes other than mineral and skeletal homeostasis, given that CaSR and $GABA_{B1}$R are expressed in neurons and many other peripheral tissues.

Shimona Starling

ORIGINAL ARTICLE Chang, W. et al. PTH hypersecretion triggered by a $GABA_{B1}$ and Ca^{2+}-sensing receptor heterocomplex in hyperparathyroidism. *Nat. Metab.* https://doi.org/10.1038/s42255-020-0175-z (2020)

ENDOCRINE DISRUPTORS

Maternal paraben exposure and childhood weight gain

Parabens are alkyl esters with antimicrobial activity that are widely used as preservatives in cosmetics, food, toiletries and medications. Irina Lehmann, Tobias Polte and colleagues have published a new study in *Nature Communications* showing that maternal exposure to parabens triggers childhood overweight development.

"Parabens are considered to be endocrine disrupting chemicals just like phthalates or bisphenol A; however, whether low-dose paraben exposure could cause adverse health effects has been a controversial topic in the past few years," explain Lehmann and Polte. "The prenatal period is a sensitive time window for chemical exposure, therefore we decided to focus in the present study on maternal exposure to parabens and its effect on children's body weight development."

The researchers examined epidemiological evidence of the effects of paraben exposure from the LINA prospective cohort of 629 mother–child pairs. Mothers reported their use of 'leave-on' and 'rinse-off' cosmetic products during pregnancy by questionnaire and maternal paraben exposure was assessed by measurements of urine. Notably, mothers reporting use of paraben-containing leave-on products had threefold higher levels of urinary parabens than mothers using paraben-free products. Adjusted logistic regression models were applied to data from LINA to examine associations between prenatal paraben exposure, child birth weight and weight gain in childhood. High prenatal maternal exposure to long-chain butylparabens (BuPs) increased the risk of overweight in early to mid-childhood.

To investigate potential mechanisms, the researchers conducted in vivo studies of BuP exposure in mice. Female offspring from perinatally nBuP-exposed dams showed 20–45% increased weight gain over the study, compared with 10% gain in control animals. Moreover, female offspring in the nBuP group had increased food intake. No weight differences were seen in male offspring. Importantly, urinary nBuP concentrations from exposed dams were measured and found to be in the same range as the LINA cohort.

Further analyses of female offspring from nBuP-exposed dams showed reduced hypothalamic expression of leptin receptor (*Lepr*) and pro-opiomelanocortin (*Pomc*) mRNA along with hypermethylation of a regulatory region of *Pomc* (nPE1). These findings suggest that BuP might affect central regulation of hunger.

"We are currently lacking mechanistic explanations for the initial molecular events at the placental–fetal interface and how prenatal exposure to BuP or other oestrogenic compounds might lead, for example, to an altered epigenetic profile and an increased risk of childhood overweight," conclude Lehmann and Polte. "Thus, further studies are needed to reproduce our epidemiological findings and bring more light into the very early mechanisms behind this association."

Shimona Starling

Credit: Brian Hagiwara/Getty

ORIGINAL ARTICLE Leppert, B. et al. Maternal paraben exposure triggers childhood overweight development. *Nat. Commun.* **11**, 561 (2020)