NEUROENDOCRINOLOGY

Mapping neuron functions in the gut–brain axis

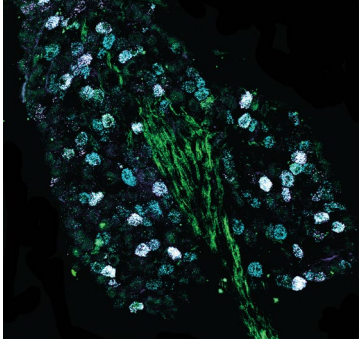
Gut-innervating sensory neurons are essential for regulation of satiety and blood levels of glucose after food consumption. However, the precise functions of different populations of these neurons are poorly understood. A recent *Cell Metabolism* article interrogated the locations and functions of several molecularly defined gut-innervating neuron populations.

The authors developed triple transgenic mouse models to fluorescently label sensory neurons expressing one of four genetic markers: *Phox2b*, *Wnt1*, *Glp1r* or *Gpr65*. *Phox2b* expression is found in vagal afferents, whereas *Wnt1* is expressed in spinal afferents, so the authors used these mouse lines to map the location of vagal and spinal afferent innervation in the gastrointestinal tract. Vagal afferents primarily innervated the muscular and mucosal layers of the stomach and upper small intestine. By contrast, spinal afferents were more present in the lower gut, particularly the colon crypts.

The researchers then investigated two populations of vagal afferents, expressing either *Glp1r* (GLP1R-neurons) or *Gpr65* (GPR65-neurons). "These two genetically distinct vagal sensory neuron populations, which selectively innervate the gut, differently control glucose tolerance and hepatic glucose production," explain authors Diba Borgmann and Elisa Ciglieri.

Through selective activation or inhibition of GLP1R-neurons or GPR65-neurons, the authors found that GLP1R-neurons mediated appetite suppression and improved glucose tolerance. By contrast, GPR65-neuron activation led to increased hepatic glucose production. Inhibition of GLP1R-neurons reversed the improvement in glucose tolerance seen after injection of the enteric hormone CCK, suggesting that CCK activates GLP1R-neurons to improve glucose tolerance.

> "CCK activates GLP1R-neurons to improve glucose tolerance"



Nodose ganglion with different distinct sensory neurons labelled. Image courtesy of Max Planck Society for Metabolism Research.

The authors believe that studying neuronal populations of the gut–brain axis could help develop therapies to treat obesity. "We hope that our findings lay the foundation for future research on deciphering the role of gut-innervating sensory neurons in impaired satiety signalling and compromised glycaemic control in individuals with obesity," corresponding author Henning Fenselau concludes.

Olivia Tysoe

ORIGINAL ARTICLE Borgmann D. et al. Gut-brain communication by distinct sensory neurons differently controls feeding and glucose metabolism. *Cell Metab.* https://doi.org/10.1016/j.cmet.2021.05.002 (2021)

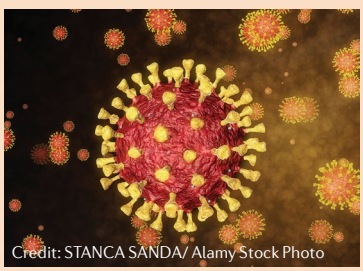
METABOLISM

How COVID-19 disrupts glycometabolic control

Coronavirus disease 2019 (COVID-19) is associated with hyperglycaemia. A study published in *Nature Metabolism* now shows how hyperglycaemia develops in a cohort of 551 patients hospitalized with COVID-19 in Italy.

"We started from a clinical observation: in patients hospitalized for COVID-19, there is a huge rate of new-onset hyperglycaemia," explains corresponding author Paolo Fiorina. "In these patients, clinical outcomes are the poorest, with more requirement for ventilation, need of ICU and longer length of hospitalization." Of note, these patients did not have pre-existing diabetes mellitus, as their levels of HbA_{1c} were normal.

> "Patients with COVID-19 also showed changes in the cytokine secretome"



Credit: STANCA SANDA/ Alamy Stock Photo

In patients with new-onset hyperglycaemia at hospital admission for COVID-19, persistent hyperglycaemia (6 months) was observed in 35%, diabetes mellitus was diagnosed in ~2% and the remaining patients became normoglycaemic. Continuous glucose monitoring was used in a small number of patients with COVID-19 to confirm the impaired glycaemic profile. Importantly, this approach showed some glycaemic alterations also persisted in some of those who had recovered from COVID-19.

The serum hormone profile (tested under fasting conditions and arginine stimulation) was altered in patients with COVID-19 and patients who had recovered from COVID-19. These changes demonstrated persistent insulin resistance and suggested that β-cell hyperstimulation might be occurring in COVID-19.

Patients with COVID-19 also showed changes in the cytokine secretome, which persisted long after recovery. Of note, using tocilizumab (anti-IL-6) to treat patients with COVID-19, new-onset hyperglycaemia and high levels of IL-6 reduced glycaemia. This preliminary finding suggests a mechanistic link between disrupted cytokines and glycaemia in COVID-19. "Our data demonstrate that COVID-19 is associated with aberrant glycometabolic control, which can persist even after recovery," concludes Fiorina. "These data suggest that further investigation of metabolic abnormalities in the context of long COVID is warranted."

Shimona Starling

ORIGINAL ARTICLE Montefusco, L. et al. Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. *Nat. Metab.* https://doi.org/10.1038/s42255-021-00407-6 (2021)
RELATED ARTICLE Lim, S. et al. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat. Rev. Endocrinol.* **17**, 11–30 (2021)