Credit: Jennie Vallis/Springer Nature Limited

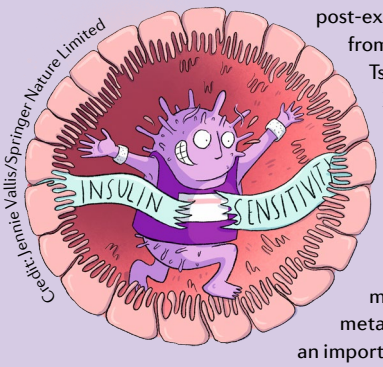
> the mechanisms by which circadian misalignment affects metabolism differ between women and men

had a marked increased hedonic appetite with increased cravings for energy-dense and savoury foods under the same circadian misalignment conditions."

These data highlight the importance of further studies into the sex-specific effects of circadian misalignment.

Alan Morris

ORIGINAL ARTICLE Qian, J. et al. Sex differences in the circadian misalignment effects on energy regulation. *Proc. Natl Acad. Sci. USA* **116**, 23806–23812 (2019)



Credit: Jennie Vallis/Springer Nature Limited

post-exercise microbiomes from responders," report Tse, Panagiotou and Xu. No such changes were seen in the mice that received a transplant from non-responders.

"Our study suggests that the microbiota and its metabolites serve as an important contributor to the metabolic benefits of exercise interventions and also identifies maladaptation of gut microbiota as a 'culprit' for those individuals who do not respond to exercise intervention," conclude Tse, Panagiotou and Xu. The researchers are now planning to expand their study by including different communities, male and female participants, participants from a wide range of ages and different forms of exercise.

> the microbiota and its metabolites serve as an important contributor to the metabolic benefits of exercise interventions

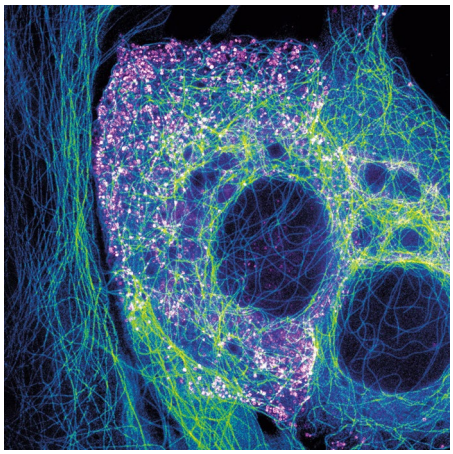
Claire Greenhill

ORIGINAL ARTICLE Liu, Y. et al. Gut microbiome fermentation determines the efficacy of exercise for diabetes prevention. *Cell Metab.* https://doi.org/10.1016/j.cmet.2019.11.001 (2019)

ISLET BIOLOGY

Pulsatile GABA secretion by β-cells

In islets of Langerhans, the neurotransmitter γ-aminobutyric acid (GABA) acts as a paracrine and autocrine signal that regulates hormone release; however, the mechanisms by which β-cells secrete GABA are unclear. A study by Steinunn Baekkeskov, Alejandro Caicedo, Edward Phelps and colleagues highlights a new mechanism for pulsatile GABA secretion from cytosolic pools in β-cells.



A super-resolution image of a human β-cell obtained by stimulated emission depletion microscopy with α-tubulin coloured green and insulin coloured magenta. Image courtesy of Edward A. Phelps, École Polytechnique Fédérale de Lausanne, Switzerland, and University of Florida, USA.

In neurons, GABA is released via a secretory vesicular pathway; however, β-cells lack a vesicular GABA transporter. "Using up-to-date microscopy techniques, we surprisingly observed that GABA in human and rodent β-cells is almost entirely cytosolic," says Baekkeskov, "which was an unexpected result that was difficult to synthesize with a neuron-like mode of vesicular GABA release." Interestingly, cytosolic pools of GABA were depleted in pancreatic islets obtained from cadaveric human donors with either type 1 or type 2 diabetes mellitus, compared with islets from non-diabetic donors.

"A major challenge was to determine GABA release from human islets in real time," explains Caicedo. "To this end, we used a method based on sniffer cells, which express receptors for GABA that, when activated, increase Ca^{2+} levels inside the cell." Using the sniffer cells, the team were able to show that GABA is secreted from islets in a pulsatile fashion. Moreover, secretion depended on GABA content; that is, decreasing GABA levels decreased secretion and vice versa.

Analysis of available RNA sequencing datasets of human islets to identify GABA transporters, followed by functional studies, identified two proteins that transport cytosolic GABA across the plasma membrane in β-cells: VRAC, which facilitates efflux, and TauT, which mediates uptake.

Next, using multiple complementary methods, the researchers showed that secretion of endogenous GABA from the cytosolic β-cell pool decreased insulin release and also stabilized the periodicity of glucose-responsive insulin secretion. Finally, GABA secretion in human islets from donors with type 1 or type 2 diabetes mellitus was examined. Diabetes mellitus was associated with disrupted cytosolic GABA secretion, hinting at a new potential mechanism of diabetes mellitus development.

"Our paper reveals a novel mechanism for GABA release from β-cells, namely VRAC-mediated GABA release," concludes Phelps. "This research poses important new questions, including whether there is still a role for secretory vesicle release of GABA in β-cells and what the mechanism is that drives the pulsatile nature of cytosolic GABA being released from the β-cells."

Shimona Starling

ORIGINAL ARTICLE Menegaz, D. et al. Mechanism and effects of pulsatile GABA secretion from cytosolic pools in the human beta cell. *Nat. Metab.* **1**, 1110–1126 (2019)