Study uncovers key cause of type 2 diabetes

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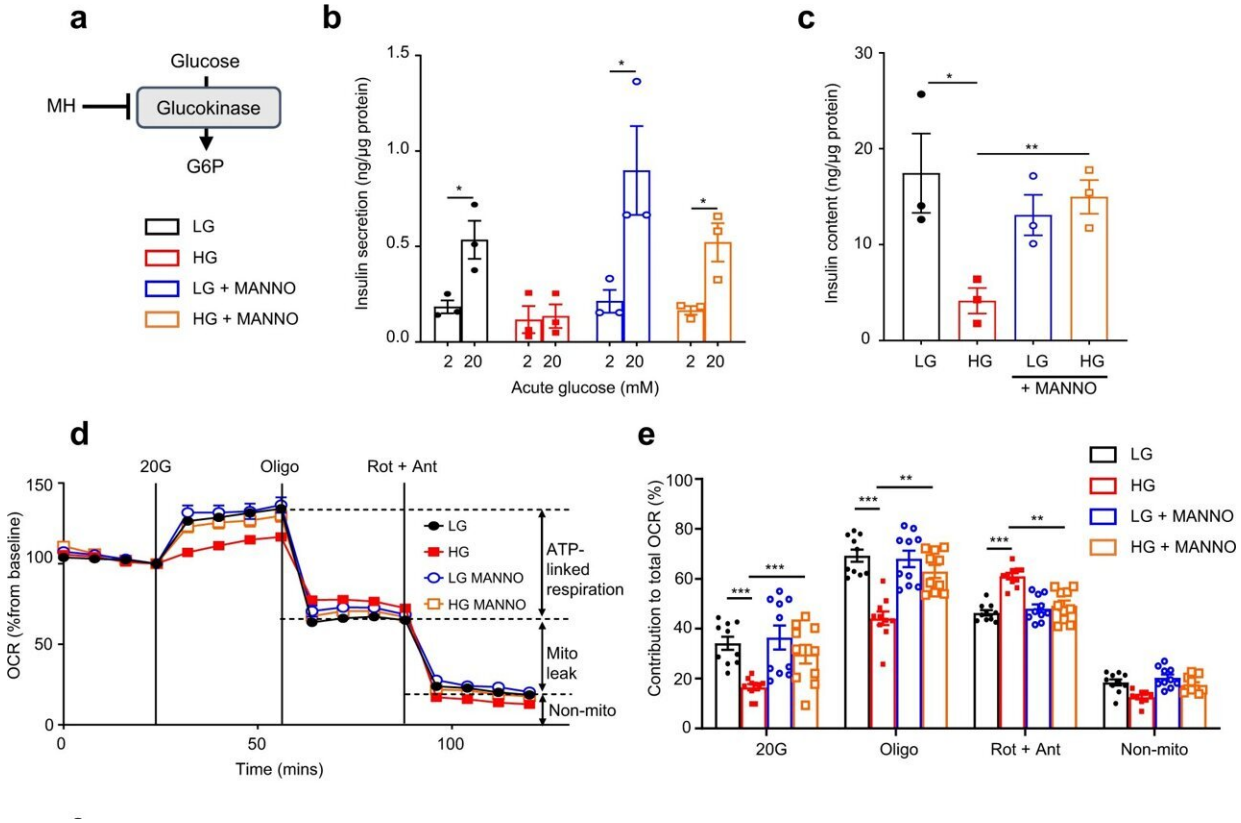

Inhibition of glucokinase prevents the effects of chronic hyperglycaemia. **a** Schematic showing how mannoheptulose (MH) inhibits glucose metabolism. **b**, **c** Insulin secretion (**b**) and insulin content (**c**) in LG-cells and HG-cells cultured for 48 h ± 10 mM mannoheptulose (MANNO) and then stimulated with 2 mM or 20 mM glucose. Mannoheptulose was omitted during the assay (n = 3 biologically independent experiments). **d** Oxygen-consumption rate (OCR) in LG-cells and HG-cells cultured for 48 h ± 10 mM MANNO. OCR was recorded at 2 mM glucose and after sequential addition of 20 mM glucose (20 G), 1 µM oligomycin (Oligo) and 0.5 µM rotenone + 0.5 µM antimycin A (Rot + Ant). Data are expressed as the percentage change from baseline (2 mM glucose); n = 10

biologically independent experiments per group. **e** Percentage change in OCR when glucose was raised from 2 to 20 mM (20 G), ATP-linked OCR (Oligo), OCR required to maintain the mitochondrial leak (Rot + Ant) and non-mitochondrial OCR (non-mito); $n = 10$ biologically independent experiments per group. Same data as in (**d**). **f**, **g** mRNA levels of the indicated genes involved in glycolytic (**f**) and mitochondrial (**g**) metabolism as assessed by qPCR in LG-cells and HG-cells cultured for 48 h ± 10 mM mannoheptulose (*Pdk1, Idh2* and *Ndufs8*, $n = 6$ biologically independent experiments; *Ndufa4*, $n = 4$ biologically independent experiments; *Pfkl*, *Pfkfb3*, *Eno1*, *Sdha* and *Mdh2*, $n = 3$ biologically independent experiments; *Aldob*, $n = 6$ biologically independent experiments for LG and HG but $n = 5$ for LG + MANNO and HG + MANNO; *Ndufs8*, $n = 6$ biologically independent experiments for LG but $n = 3$ for LG + MANNO, HG and HG + MANNO). All panels show individual data points and mean ± s.e.m. $*P$