Extended Figure 1 Effect of MC3R Loss-of-Function (LoF) mutations on height (cm) across time

Carriers of MC3R LoF mutations (dark blue) had lower height throughout early life course compared to the reference group (light blue) after adjusting for sex and age. Figures only show results where the mutation group was represented by at least one individual at all time points between birth and 24 years. Error bars represent 95% confidence intervals.
Extended Data Figure 2 MC3R is essential for normal cycle length and for fasting-induced suppression of the reproductive axis.

(a & b) Representative traces of progression through the oestrous cycle in a (a) WT and (b) Mc3r−/− mouse following an overnight fast. D=Dioestrous; M=Metoestrous; E=Oestrous.
Extended Figure 3 Mc3r is expressed in several cell populations in the mouse hypothalamus
(a) T-SNE plot showing 28 neuronal clusters of the mouse hypothalamus from a combined dataset consisting of 18427 neurons from 4 published studies. Gene markers are available in Table S8.
(b) Mc3r is expressed in several neuronal populations (log2 normalised expression in dark red).
(c) Multiplexed smFISH showing the co-expression of Mc3r (white) Kiss1 (red) and Tac2 (green) in the arcuate nucleus.
(d) Venn diagram showing the number of cells expressing Kiss1 (left), Tac2 (right), or both (KNDy, centre).
(e) Violin plots showing the number of Mc3r mRNA puncta in Kiss1 only, KNDy, and Tac2 only cells. Mean percentage of cells ± SEM with detected Mc3r is shown. N=3
(f) Expression of Mc3r (white) in Ghrh (yellow) positive cells in the arcuate nucleus and the dorsal paraventricular hypothalamus (PVH). Tac2 (magenta).
(g) Violin plots showing number of Mc3r mRNA puncta in GHRH neurons from the two regions.
Extended Data Figure 4 Expression of *Mc3r* and *Lepr* in KNDy and GHRH neurons

(a - b) *Mc3r* expression is more prominent compared to *Mc4r* and *Lepr* in (a) *Tac2* (KNDy) (cluster 7, blue) and (b) GHRH neurons (cluster 15, green).

(c) Violin plots showing expression of *Kiss1*, *Tac2*, *Ghrh*, *Mc3r* and *Lepr* in KNDy and GHRH neurons in the Campbell	extsuperscript{39} and the Chen	extsuperscript{43} dataset in separate. The Lam	extsuperscript{41} and Romanov	extsuperscript{42} datasets are not showed due to low cell count (<10) in either clusters.
Extended Data Figure 5 Annotated overviews showing the co-expression of MC3R, KISS1, and GHRH in the human hypothalamic arcuate nucleus

(a) Co-expression of MC3R and KISS1 was detected using smFISH: MC3R = grey, KISS1 = magenta and MC3R+KISS1 = white. The white square marks the representative example shown in Fig 4e (Scale bar = 200um)

(b) Co-expression of MC3R and GHRH was detected using smFISH: MC3R = grey, GHRH = green and MC3R+KISS1 = white. The white square marks the representative example shown in Fig 4f (Scale bar = 200um)
Extended Data Figure 6 Mc3r expression in kisspeptin neurons in the mouse hypothalamus at P16, P28 and P48

(a-c) smFISH showing the co-expression of Mc3r and Kiss1 in the anteroventral periventricular nucleus (AVPV) at (a) post-natal day (P)16; (b) P28 and (c) P48: Mc3r = green, Kiss1 = red (Scale bar = 20um).