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Obesity due to melanocortin 4 receptor (MC4R) deficiency is associated with delayed gastric emptying

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Abstract

Objective: People who are severely obese due to melanocortin-4 receptor (MC4R) deficiency experience hyperphagia and impaired fullness after a meal (satiety). Meal-induced satiety is influenced by hormones, such as peptide-YY (PYY), which are released by enteroendocrine cells upon nutrient delivery to the small intestine.

Design: We investigated whether gastric emptying and PYY levels are altered in MC4R deficiency.

Methods: Gastric emptying was measured with a gastric scintigraphy protocol using technetium-99m ($^{99}Tc^{m}$)-Tin Colloid for 3.5 h in individuals with loss of function *MC4R* variants and a control group of similar age and weight. In a separate study, we measured plasma PYY levels before and at multiple time points after three standardised meals given to individuals with MC4R deficiency and controls. Fasting PYY (basal secretion) and postprandial PYY levels were measured and the area under the curve and inter-meal peak were calculated.

Results: We found that gastric emptying time was significantly delayed and percentage meal retention increased in individuals with MC4R deficiency compared to obese controls. In addition, fasting and mean PYY secretion throughout the day were decreased in MC4R deficiency, whereas postprandial PYY secretion was unaltered.

Conclusion: Delayed gastric emptying and reduced basal PYY secretion may contribute to impaired satiety in people with obesity due to MC4R deficiency.

KEYWORDS

gastric emptying, MC4R, obesity, PYY

1 | INTRODUCTION

Melanocortin-4 receptor (MC4R) signalling plays a pivotal role in the regulation of body weight and genetic disruption of *MC4R* causes hyperphagia and severe obesity in mice and humans.[1,2] Heterozygous loss of function mutations in *MC4R* represent the commonest monogenic form of obesity and are found in 2%–5% of severely obese children and adults in multiple populations.[2,3] The effects of MC4R signalling on hunger and the drive to eat are predominantly mediated by neuronal circuits in the hypothalamus, where stimulation

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of MC4R expressing neurons by the endogenous agonist α-melanocyte-stimulating hormone (α-MSH) leads to a reduction in food intake in the fed state.[4] MC4R is also highly expressed in the dorsal motor nucleus of the vagus (DMV), the site of preganglionic parasympathetic vagal efferent neurons that innervate the gastrointestinal system and in the nucleus tractus solitarius (NTS) and nodose ganglion, sites that receive vagal afferents from the stomach and duodenum.[5] Administration of melanocortin agonists into the NTS or DMV inhibits food intake and decreases phasic gastric contractions, suggesting a role in gastric motility and meal-induced satiety.[5,6] Interestingly, a large study of people carrying a common noncoding obesity-associated genetic variant that lies downstream of *MC4R* (rs17782313) found that this variant was associated with delayed gastric emptying.[7]

MC4R is also expressed in enteroendocrine cells[8]; a subset of these cells release peptide-YY (PYY) in response to nutrient delivery to the small intestine. Infusion and functional imaging studies have shown that PYY administration to healthy volunteers leads to satiety by activating brainstem neural circuits.[9–11] Here, we studied individuals with heterozygous loss of function mutations in MC4R and a control group of similar age and weight. We first used technetium-labelled gastric scintigraphy,[12] which relies on the labelling of foods to measure both the solid and liquid phases of gastric emptying. In a second study, we studied basal and postprandial PYY in people with loss of function mutations in *MC4R* and obese controls.

2 | METHODS

2.1 | Participants

All studies were approved by the Cambridge Local Research Ethics Committee and each subject provided written informed consent. People with MC4R mutations were identified by Sanger sequencing of all participants in the Genetics of Obesity Study (GOOS), a cohort of >7000 individuals with severe early-onset obesity defined as a body mass index (BMI; weight in kilograms divided by the square of the height in metres) standard deviation score greater than 3; onset less than 10 years.[2,13] None of the participants were taking anti-obesity medication or dietary treatment for weight loss. Data were compared with controls of same sex and similar age and BMI with a normal MC4R genotype recruited through public advertisement.

Details on participants in the gastric emptying study are provided in Table 1 and for the PYY secretion study in Table 2. Pregnant and breastfeeding women were excluded from the study. The studies were conducted at the Wellcome-MRC Institute of Metabolic Science Translational Research Facility and the Nuclear Medicine Department, Addenbrooke's Hospital, Cambridge.

TABLE 2 MC4R-deficient participants and obese controls in the postprandial PYY study

MC4R variant	Age (years)	BMI (kg/m^2)
F280AfsX12 (het)	40.6	41.3
T112NfsX11 (het)	25.4	43.3
T112NfsX11 (het)	20	67.3
C271Y (het)	39.8	44.3
C271Y (het)	42.7	41
I125K (het)	21.5	32
Obese control	37.9	44.1
Obese control	65.2	35.8
Obese control	71.8	43.5
Obese control	42.0	40.9
Obese control	59.4	38.5

Abbreviation: PYY, peptide-YY; MC4R, melanocortin 4 receptor.

TABLE 1 Baseline characteristics of study participants in the gastric emptying study

	Sex		Age (years)		BMI (kg/m^2)		Fasting glucose (mmol/l)	
MC4R Variant	MC4R	Control	MC4R	Control	MC4R	Control	MC4R	Control
I125K (het)	M	M	27.5	25.6	47.1	43.8	4.5	5.9
C271Y (het)	F	F	20.2	33.6	52.1	55.4	5.3	5.4
Y35X; D37V (het)	F	F	31.2	20.8	32.7	33.6	4.8	4.8
A68V (het)	M	M	51.2	38.9	27.1	29.4	4.8	5.8
C271Y (het)	F	F	24.3	30.4	38.4	38.4	4.1	4.3
D122Y (het)	M	M	41.2	40.9	39.5	36.3	4.9	5.4
L211MfsX6; P299H (het)	M	M	34.9	35.0	24.2	28.6	4.8	5
R165Q	M	M	45.2	40.0	22.6	23.9	4.2	4.8
Q115EfsX7	M	M	33.6	36.4	40.1	38.3	4.5	3.8

Abbreviation: BMI, body mass index; MC4R, melanocortin 4 receptor.

2.2 | Study design gastric emptying study

Study participants for this study were not taking opiates, prokinetics, anticholinergics or any medication affecting the central nervous system or gastrointestinal motility; they did not have disorders affecting the gastrointestinal tract. A wide variety of radionuclide markers have been used to follow gastric emptying. Solid-phase radionuclide markers must have a high labelling efficiency, and the radiolabel must not elute from the food material during the procedure. The most frequently used solid-phase marker is labelled eggs. In this study, 11 MBq $^{99}Tc^{m}$-Tin Colloid was added to two egg whites, according to standardised criteria.[12] Oral $^{99}Tc^{m}$-Tin Colloid is a nonabsorbable tracer with very low tissue radiation exposure.[14] The eggs were allowed to incubate for 5 min then scrambled and cooked in a pan until firm. After a 6-h fasting period, all participants consumed a standardised meal consisting of 120 g scrambled egg white, two slices of toasted white bread, 30 g jam and 120 ml water, as the stomach needs a working volume of food to demonstrate normal emptying processes. Participants were asked to consume the radio-labelled meal within 10 min before the first anterior and posterior images were obtained with a gamma camera (GE Discovery 630). Then images were taken at 15-min intervals during the first 2 h and at 30-min intervals for the next 1.5 h. The study was completed 3.5 h after the consumption of the radio-labelled meal. For the analysis, regions of interest were drawn and geometric means of decay-corrected counts were determined at each time point to estimate the proportion of 99m-Tc from the stomach. All gastric emptying data were analysed by two investigators blinded to genotype. Several fits were tested: the mono-exponential fit was necessary and sufficient to provide an optimal R^2. The bi-exponential fit did not improve the quality of the fit. Times, when 10%, 50% (t1/2), and 90% of the meal was emptied, were determined for each participant. Discrete variables are expressed as the percentage of the initial counts remaining in a region of interest (ROI) drawn around the stomach and continuous variables as median (interquartile range [IQR]). Raw counts (median and interquartile range) are provided in Table 3.

TABLE 3 Raw counts (median, interquartile range [IQR]) for all time points

Time points	Raw counts (median, IQR)	
	MC4R	Controls
T1	8061 (6770–12838)	7842 (6432–12117)
T2	7526 (5579–11291)	6701 (6313–11959)
T3	6832 (4655–10391)	7235 (4580–9517)
T4	6207 (3403–8547)	5607 (3652–7906)
T5	5514 (2647–7137)	4297 (3035–7070)
T6	4719 (1973–6543)	3195 (2383–5864)
T7	4422 (1635–5935)	2829 (2001–4363)
T8	3730 (1256–5242)	2318 (1529–3407)
T9	3474 (1065–4643)	1833 (1144–2600)
T10	2240 (734–3347)	908 (569–1683)
T11	1509 (332–2344)	243 (175–1010)
T12	1045 (197–1497)	170 (121–423)

2.3 | Study design gut hormone study

All subjects in this study had normal levels of lipids, glucose and thyroid hormones. None of the participants had been diagnosed with diabetes mellitus or gastrointestinal disease, and subjects were not taking any medications. In addition, obese controls had a normal MC4R genotype and no history suggestive of other known monogenic obesity syndromes. PYY concentrations were obtained during a 12-h sampling period with three meals standardised for macronutrient and caloric content after a 10-h overnight fast. Meals were provided at 8 a.m., noon, and 5:30 p.m. Blood was drawn every half hour from 7:30 a.m. to 8:30 p.m. Meals were calculated to provide 20%, 35% and 35% of daily individual energy requirements (breakfast, lunch and dinner, respectively) using the Schofield formula.[15] The macronutrient content of the meals was 20% protein, 30% fat and 50% carbohydrates and energy content ranged from 400 to 600 Calories. Visual analogue scales (VAS), which require respondents to specify their level of hunger or fullness by indicating a position along a continuous line between two end-points (not hungry, most hungry you have ever been; not full, most full you have ever been), were used to assess hunger and fullness every 30 min starting from 07:30 h. Blood for the measurement of PYY levels was collected from an indwelling intravenous catheter in EDTA heparin tubes. Blood was spun immediately at 4°C, and plasma was frozen and stored at −80°C until analysis. Plasma PYY levels were measured using an established in-house radioimmunoassay (RIA) described previously.[11] The detection limit was 2.5 pmol/L with an intra-assay coefficient variation of 5.8%. As some indwelling cannulas failed, we have PYY measurements up to 7:00 PM for all participants and these were included in the analysis.

2.4 | Statistical analysis

The Fisher's exact test was used for categorical data and unpaired *t* tests or the Mann–Whitney *U* test for continuous data to compare changes across groups. *p*- < .05 was defined as significant. Data were analysed using GraphPad Prism Version 7 (GraphPad Software Inc).

3 | RESULTS

3.1 | Gastric emptying

Nine people carrying a mutation in MC4R (cases) and nine controls were included in this study (Table 1). Cases and controls were

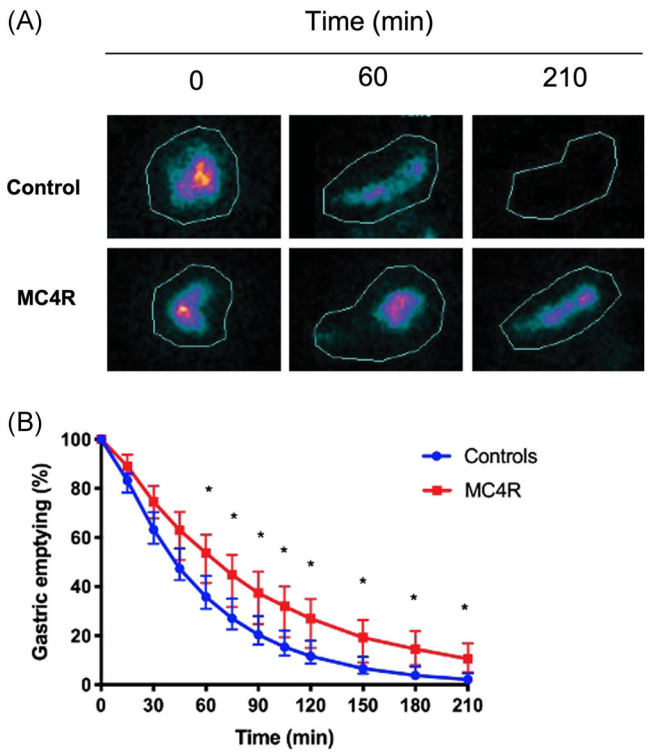

FIGURE 1 Gastric emptying in people with melanocortin 4 receptor (MC4R) deficiency and controls. (A) Illustrative scintigraphic images of gastric emptying over 3.5 h in a representative participant with a heterozygous loss of function mutation in *MC4R* and healthy control. (B) Exponentially fitted gastric emptying time in people with heterozygous loss of function mutations in MC4R and matched controls. Time-activity curve for food retention in the stomach is normalised to the activity present at time zero when the whole meal is contained within the stomach; time in minutes (min) (*$p < .05$) [Color figure can be viewed at wileyonlinelibrary.com]

comparable in age (MC4R: 33.6 [25.9–43.2] years; controls: 35.0 [28.0–39.5]), BMI (MC4R: 38.4 [25.7–43.6] kg/m^2; controls: 36.3 [29.0–41.1] kg/m^2) and sex (66.6% males in both groups). Fasting glucose levels were comparable in both groups (MC4R: 4.8 [4.4–4.9] mmol/l; controls: 5.0 [4.6–5.6] mmol/l).

We found that after consuming a meal of identical volume, 10% emptying time was significantly delayed in people with MC4R deficiency compared with controls (MC4R: 9.3 (6.2–11.4) min; controls: 5.6 (4.9–7.0) min; $p = .03$). Similarly, 50% emptying time was delayed in people with MC4R deficiency (MC4R: 61.2 (40.7–74.9) min; controls: 36.8 (32.4–45.8) min; $p = .03$) and 90% emptying time was significantly longer in people with MC4R deficiency compared to controls (MC4R: 203.2 (135.3–248.9) min; controls: 122.4 (107.7–152.1) min; $p = .03$) (Figure 1). Percentage retention at the end of the test was 9.7% (3.4–15.3) in people with MC4R deficiency compared to 2.1% (1.3–4.6) in controls ($p = .02$).

3.2 | Fasting and post-prandial PYY secretion

Six people carrying a loss of function mutation in MC4R (cases) and five controls were included in this study (Table 2). The mean age was 31.7 (20–43) years in people with MC4R deficiency and 55 (38–72) in controls. Mean BMI was 44.9 (32.0–67.3) kg/m^2 in people with MC4R deficiency and 40.6 (35.8–44.1) kg/m^2 in controls. Fasting PYY levels were 47% lower in people with MC4R deficiency compared to obese controls (9.0 ± 1.5 pmol/l vs. 16.9 ± 2.3 pmol/l, respectively, [$p = .015$], Table 4). Average PYY concentrations were also 29% lower (Table 4). To assess postprandial PYY secretion (Figure 2), several parameters were calculated: the average intermeal peak as the combined maximum value between breakfast/lunch and lunch/

TABLE 4 PYY levels in individuals with MC4R deficiency and obese controls

	Obese controls ($n = 5$)	Individuals with MC4R deficiency ($n = 6$)	p value
Fasting PYY (pmol/l)	16.9 ± 2.3	9.0 ± 1.5	.015
Mean PYY (pmol/l)	21.4 ± 0.5	15.1 ± 0.6	.00002
Area under the curve	111.1 ± 44.6	149 ± 23.2	.447
Inter-meal peak (pmol/l)	28.2 ± 12.6	20.2 ± 2.6	.217
Percentage change in PYY 30 min after all meals (%)	16.9 ± 8.3	18.6 ± 9.9	.900
Percentage change in PYY 60 min after all meals (%)	14.8 ± 8.9	18.2 ± 29.8	.922
VAS hunger scores (area under the curve)	82.2 ± 5.4	72.2 ± 6.4	.2744
VAS fullness scores (area under the curve)	140.9 ± 5.4	137.3 ± 8.3	.7369

Abbreviations: PYY, peptide-YY; MC4R, melanocortin 4 receptor; VAS, visual analogue scales.

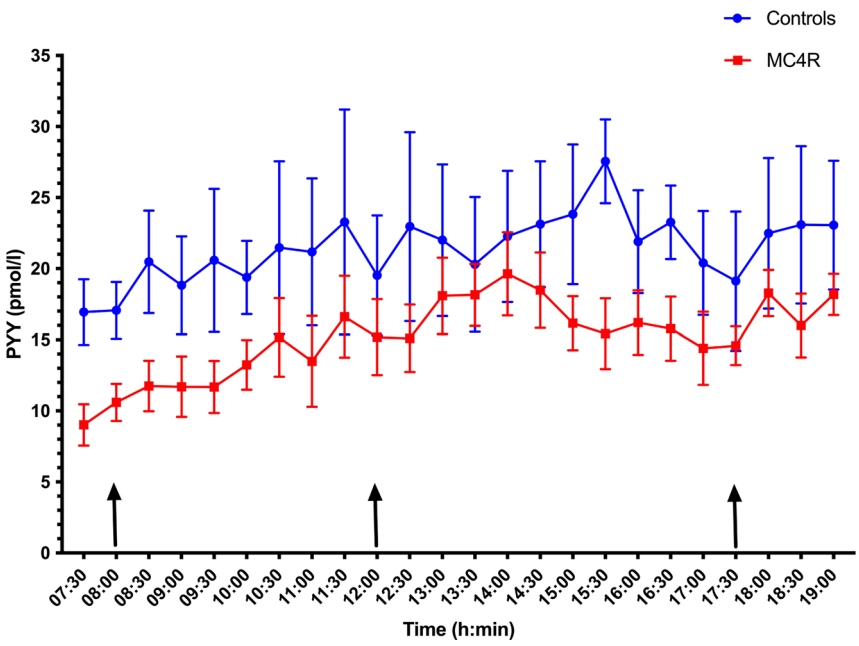

FIGURE 2 Peptide-YY (PYY) levels in relation to meals in people with melanocortin 4 receptor (MC4R) deficiency and controls. PYY concentrations in five obese subjects (blue), and six obese people with MC4R deficiency (red) during an 11:30-h sampling period with three meals standardised for macronutrient and caloric content. Meals were provided at 8 a.m., noon, and 5:30 p.m (arrows). Samples were taken every 30 min. Results are expressed as mean ± SE [Color figure can be viewed at wileyonlinelibrary.com]

dinner, the percentage change in PYY 30 min and 60 min after breakfast, lunch and dinner combined and the area under the curve (AUC) using the trapezoidal method with fasting PYY as a baseline and allowing for positive and negative peaks. There was no difference in 30 or 60 min postprandial PYY secretion, AUC or in the intermeal peak between individuals with MC4R variants ($p = .900$ for 30 min, $p = .922$ for 60 min, $p = .447$ for AUC and $p = .217$ for intermeal peak). VAS scores for hunger and fullness were not different between the two groups throughout the study period (Table 4).

4 | DISCUSSION

Here, using the gold standard method, we found that gastric emptying is delayed in people with heterozygous loss of function mutations in *MC4R*. In addition, we show that people with loss of function mutations in *MC4R* have lower basal PYY secretion. These findings warrant replication in a larger cohort, accepting the challenges of studying monogenic disorders.

Why might MC4R deficiency be associated with delayed gastric emptying? The regulation of gastric emptying involves the coordination of smooth muscle contraction driven by the enteric nervous system and the autonomic nervous system. The regulation of the gastrointestinal tract by the autonomic nervous system is complex. Whereas, in general, sympathetic tone decreases secretions and gastric motility; the parasympathetic nervous system has both inhibitory and excitatory effects on gastrointestinal tone and motility.[16] Previous studies of heart rate variability in MC4R showed greater parasympathetic activity and relatively lower sympathetic activity than in healthy controls.[17,18] In view of our findings, we suggest that autonomic dysfunction in MC4R deficiency may contribute to impaired gastric motility. Gastroparesis, defined as delayed gastric emptying in the absence of mechanical obstruction, is usually associated with symptoms of nausea, vomiting, early satiety, and bloating,[19] as commonly seen in people with autonomic dysfunction secondary to type 2 diabetes. However, the magnitude of the delay to gastric emptying seen in MC4R deficiency is modest (10% gastric retention at end of study) compared to that seen in people with diabetic gastroparesis (30% gastric retention at 4 h) and thus would not be expected to lead to marked gastrointestinal symptoms, including bloating and prolonged fullness after a meal.[20]

Gastric emptying is the major determinant of the amount of ingested nutrients that reach the small intestine, which, in turn, determines the timing and amplitude of secretion of peptide-YY (PYY), which is known to promote satiety and inhibit gastric motility.[8,11,21] In rodents, MC4Rs are the second most abundant G-protein coupled receptor on the cell membrane of PYY and GLP-1 expressing enteroendocrine L cells.[8] We found lower fasting and mean PYY levels throughout the day without a change in peak postprandial PYY secretion. MC4R signalling may affect basal PYY secretory tone but does not appear to influence the nutrient-stimulated postprandial increase in PYY, although we acknowledge that these findings are preliminary and larger studies in normal weight, obese and MC4R-deficient people are needed. Infusion of PYY has been shown to modulate brain regions involved in satiety in human functional MRI studies,[10] and therefore, a lower basal secretion could contribute to impaired satiety in MC4R deficiency. In future, it would be interesting to measure GLP-1 levels, which reflect secretion by proximal L-cells rather than distal L-cells, which secrete PYY. Given the delay in gastric emptying seen in people with MC4R deficiency, it is possible that for a lower fraction of nutrient load delivered, there is a similar stimulation of PYY release at 30 and 60 min after food intake. Also reduced gastric emptying rate in MC4R deficiency may reduce L-cell number as the converse is true in response to accelerated nutrient delivery to the small intestine after Roux-en-Y bypass surgery.[22]

In conclusion, by studying people with MC4R deficiency, we have shown that MC4R signalling modulates gastric emptying and

PYY secretion in humans. Understanding how melanocortin circuits in the brain detect and respond to gut-derived neural and hormonal signals may provide further insights into the regulation of meal-induced satiety.

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CONFLICT OF INTERESTS

The authors have no conflict of interest to declare.

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