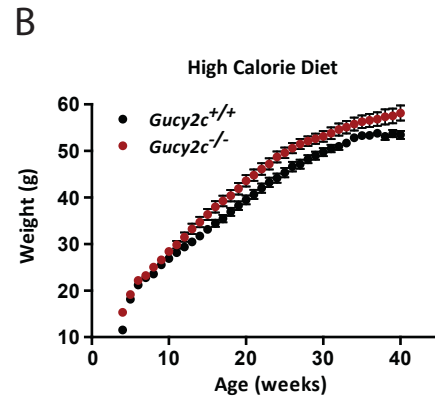
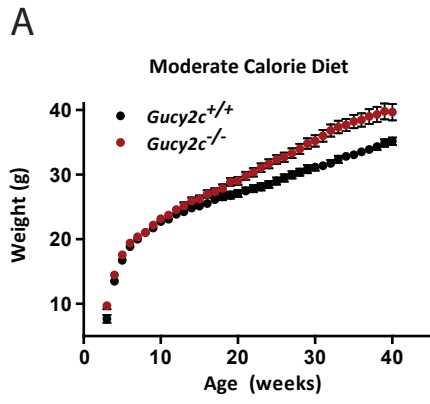
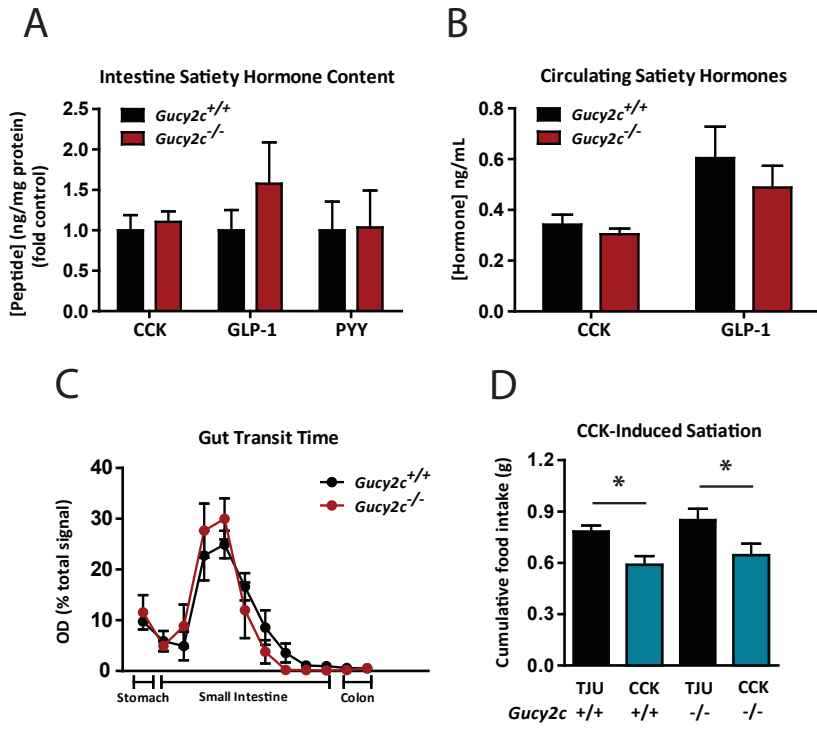


# Supplemental Figure 1

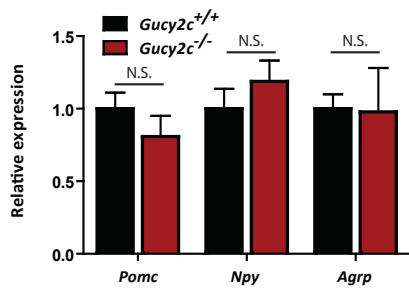


# Supplemental Figure 2

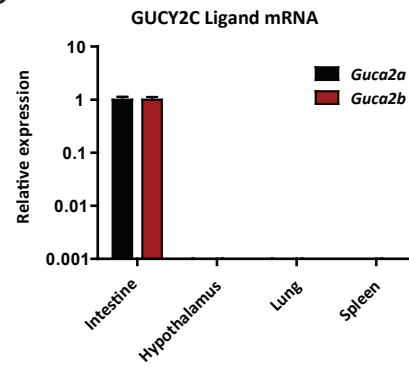


# Supplemental Figure 3

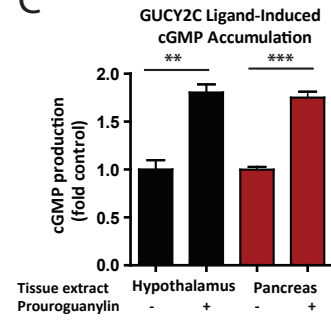
A



B



C



## Supplemental Figure Legends

**Supplemental Figure 1. (A-B)** Growth curves of male *Gucy2c*<sup>+/+</sup> and *Gucy2c*<sup>-/-</sup> mice raised on MCD (n = 20-26) and HCD (n = 27-34) (p<0.001 for all diets). All data are mean ± SEM.

**Supplemental Figure 2. (A)** Protein content of the satiety peptides CCK (jejunum), GLP-1 (ileum), and PYY (ileum) (n = 4-10) in intestine. **(B)** Circulating levels of CCK and GLP-1 in *Gucy2c*<sup>+/+</sup> and *Gucy2c*<sup>-/-</sup> mice (n = 5-10). **(C)** Gut transit of fasted mice 10 min following oral gavage with FITC-dextran + lipid (1:1) (n = 4). **(D)** Cumulative food intake of fasted *Gucy2c*<sup>+/+</sup> and *Gucy2c*<sup>-/-</sup> mice injected IV with 1 µg of TJU or CCK (n = 10 per group). All data are mean ± SEM. \* P<0.05.

**Supplemental Figure 3. (A)** Hypothalamic expression of appetite-regulating neuropeptides, normalized to β-actin (*Actb*) expression, in fasted *Gucy2c*<sup>+/+</sup> and *Gucy2c*<sup>-/-</sup> mice (n = 5 per group). **(B)** Expression of the GUCY2C ligands, guanylin (*Guca2a*) and uroguanylin (*Guca2b*), determined by qRT-PCR, normalized to *Actb* expression (n = 3). **(C)** cGMP production of CT26-GUCY2C cells treated with hypothalamic protein (350 µg), prouroguanylin (5 µg) + hypothalamic protein (350 µg), pancreatic protein (350 µg), or prouroguanylin (5 µg) + pancreatic protein (350 µg) (n = 4-10 per group). All data are mean ± SEM. N.S. = not significant (P>0.05). \*\* P<0.01, \*\*\* P<0.001.

**Supplemental Table 1. Mouse diet calorie and nutrient content.**

<b>Calorie Content</b>	<b>Low</b>	<b>Moderate</b>	<b>High</b>
<b>Protein (% energy)</b>	28.8	18.3	18.3
<b>Fat (% energy)</b>	12.7	10.2	60.9
<b>Carbohydrate (% energy)</b>	58.5	71.5	20.1
<b>Energy (kcal/g)</b>	3.08	3.78	5.16

**Supplemental Table 2. Human test meal nutrient content.**

	<b>Calories</b>	<b>Calories from Fat</b>	<b>Total Fat (g)</b>	<b>Saturated fat (g)</b>	<b>Cholesterol (mg)</b>	<b>Sodium (mg)</b>	<b>Carbohydrate (g)</b>	<b>Fiber (g)</b>	<b>Sugar (g)</b>	<b>Protein (g)</b>
<b>Eggs</b>	<b>170</b>	<b>100</b>	<b>11</b>	<b>4</b>	<b>520</b>	<b>180</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>15</b>
<b>Sausage</b>	<b>170</b>	<b>140</b>	<b>15</b>	<b>5</b>	<b>30</b>	<b>340</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>7</b>
<b>Hotcakes (3) w/ syrup</b>	<b>530</b>	<b>80</b>	<b>9</b>	<b>2</b>	<b>20</b>	<b>610</b>	<b>105</b>	<b>3</b>	<b>46</b>	<b>8</b>
<b>Hash Browns</b>	<b>150</b>	<b>80</b>	<b>9</b>	<b>1.5</b>	<b>0</b>	<b>310</b>	<b>15</b>	<b>2</b>	<b>0</b>	<b>1</b>
<b>Biscuit</b>	<b>260</b>	<b>110</b>	<b>7</b>	<b>7</b>	<b>0</b>	<b>740</b>	<b>33</b>	<b>2</b>	<b>2</b>	<b>5</b>
<b>Orange Juice</b>	<b>180</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>5</b>	<b>42</b>	<b>0</b>	<b>37</b>	<b>3</b>
<b>Total</b>	<b>1460</b>	<b>510</b>	<b>51</b>	<b>19.5</b>	<b>570</b>	<b>2185</b>	<b>197</b>	<b>7</b>	<b>85</b>	<b>39</b>

**Supplemental Table 3. Primers for quantitative RT-PCR.**

<b>Gene</b>	<b>Forward Primer</b>	<b>Reverse Primer</b>
<i>Fabp2</i>	CACACAGCTGAGATCATGGC	GCTTAGCTCTTCAGCGTTGC
<i>Dgat1</i>	CCTCAGCCTTCTTCCATGAG	ACTGGGGCATCGTAGTTGAG
<i>Dgat2</i>	GCTGAGTCCCTGAGCTCCAT	CACAAAGCCTTTGCGGTTCT
<i>Fasn</i>	AGGGGTCGACCTGGTCCTCA	GCCATGCCAGAGGGTGGTT
<i>Acadl</i>	GCTGCCCTCCGCCCCGATGTT	ATGTTTCTCTGCGATGTTGATG
<i>Acadm</i>	TGGAGACATTGCCAATCAGC	ACCATAGAGCTGAAGACAGG
<i>Glut2</i>	GTCCAGAAAGCCCCAGATACC	GTGACATCCTCAGTTCCTCTTAG
<i>Sglt1</i>	CACCATCTTGATCATCTCCTTCCT	TGCGTAGACTCCAACACAAAC
<i>Vil1</i>	CATCACTCCTCGGCTCTTCG	GTCATGCCCAAGGCCCTAGT