

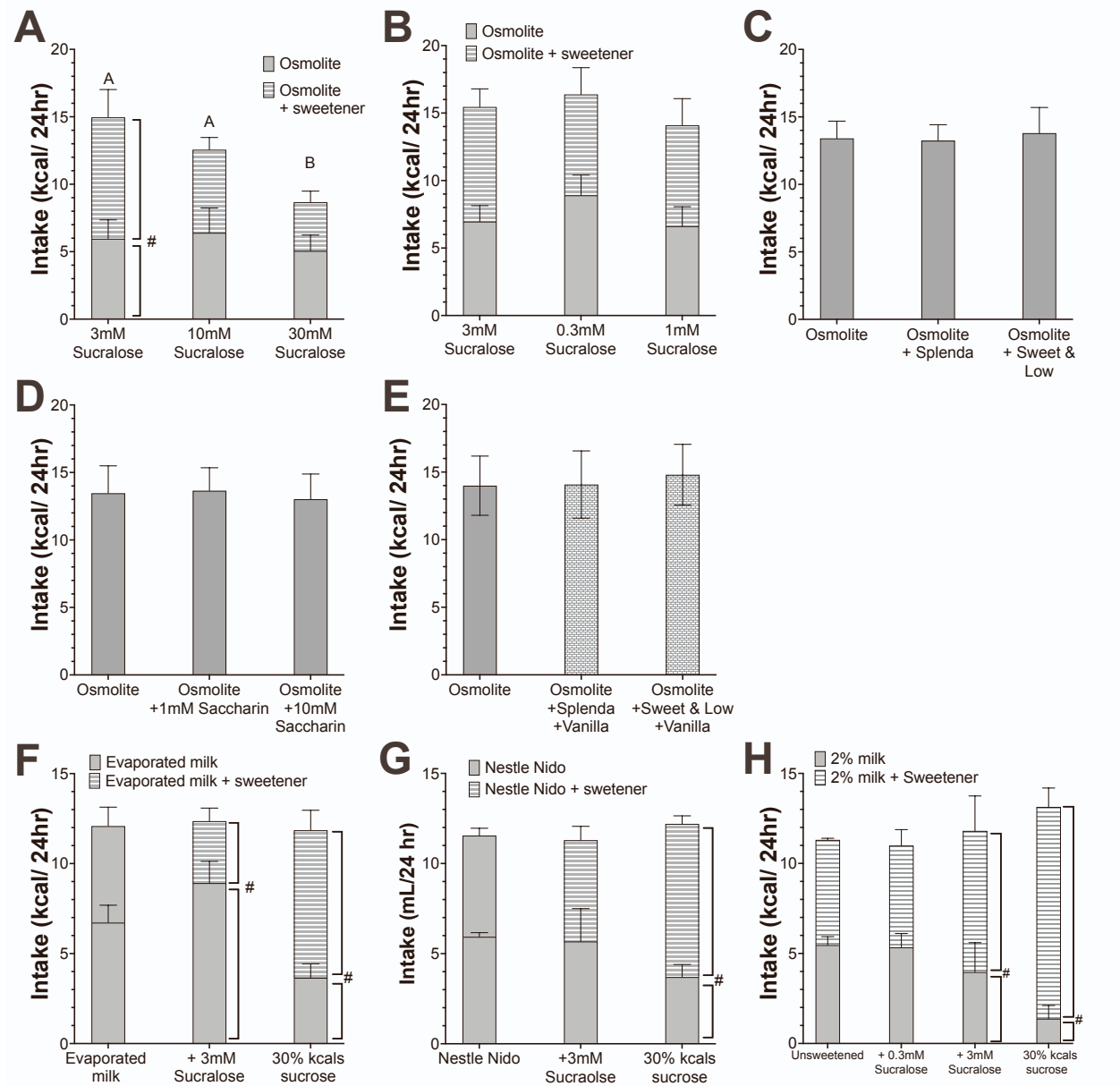
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**Supplemental information**

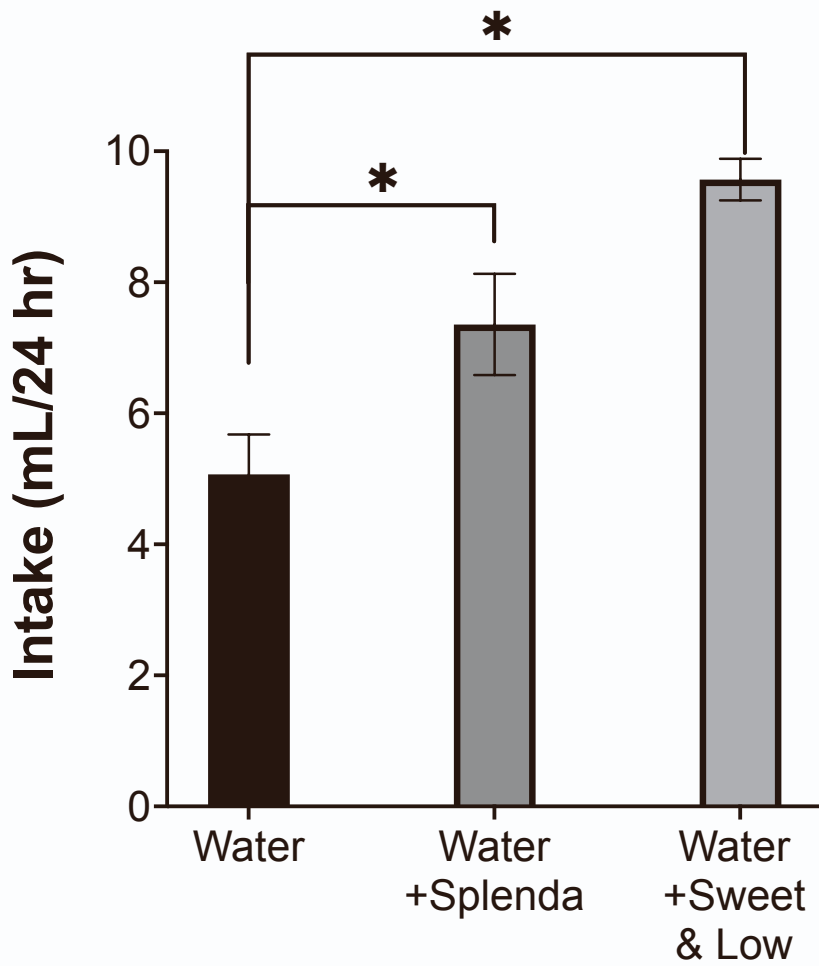
**Post-oral sensing of fat  
increases food intake  
and attenuates body weight defense**

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## Supplemental Figures

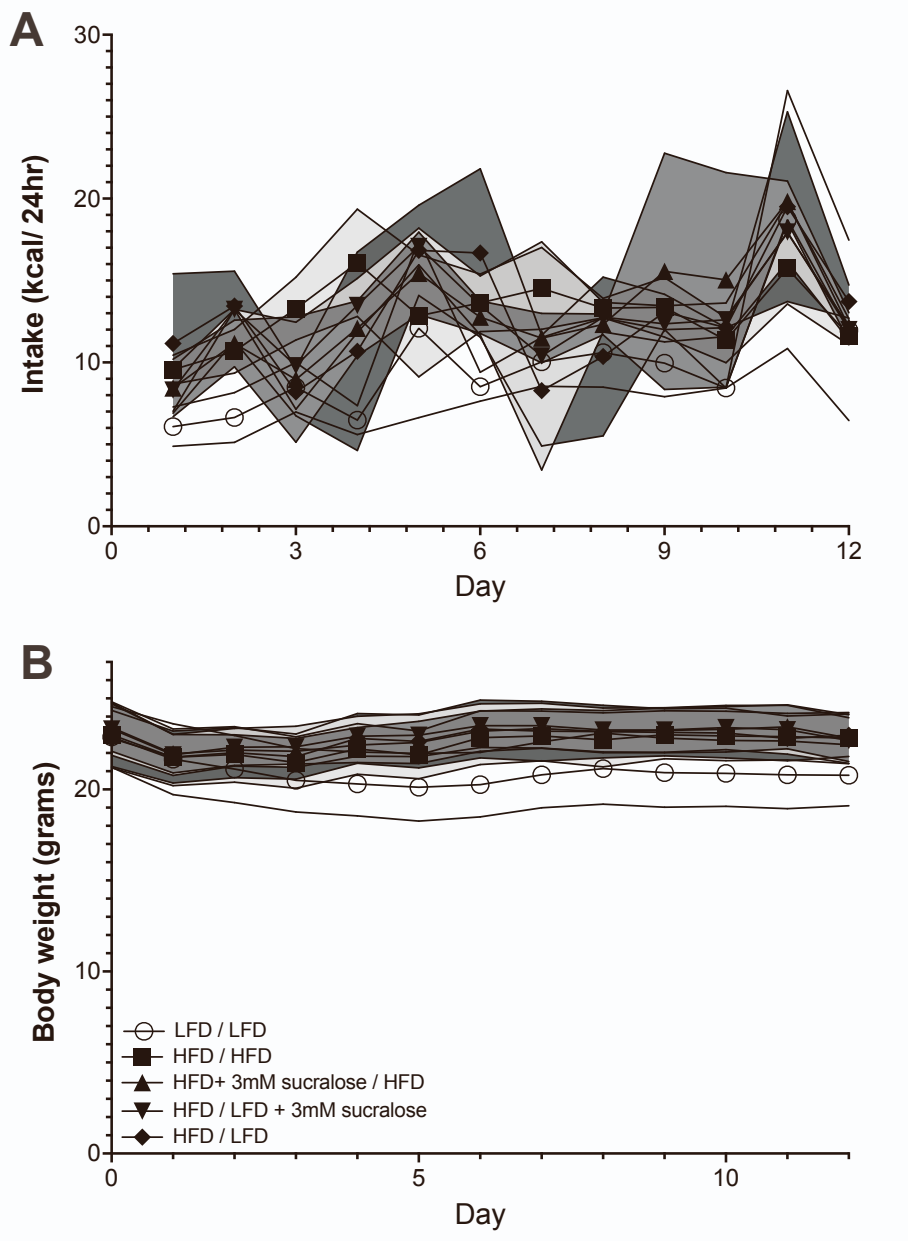


**Supplemental Figure 1. Testing diet and sweetener combinations, Related to Figure 1.** A-E) Osmolite is used as the base diet and is sweetened with sucrose, or a non-nutritive sweetener as listed and with the addition of vanilla in E. F) evaporated milk, G) Nestle Nido, H) 2% milk were offered in two choice tests. Data are presented as mean  $\pm$  standard deviation. A-B, F-H) solid colored bars show intake of unsweetened diet; striped bars show intake of sweetened diet as indicated. #  $p < 0.05$  using a paired T-test where brackets mark the comparison. N=5/group.



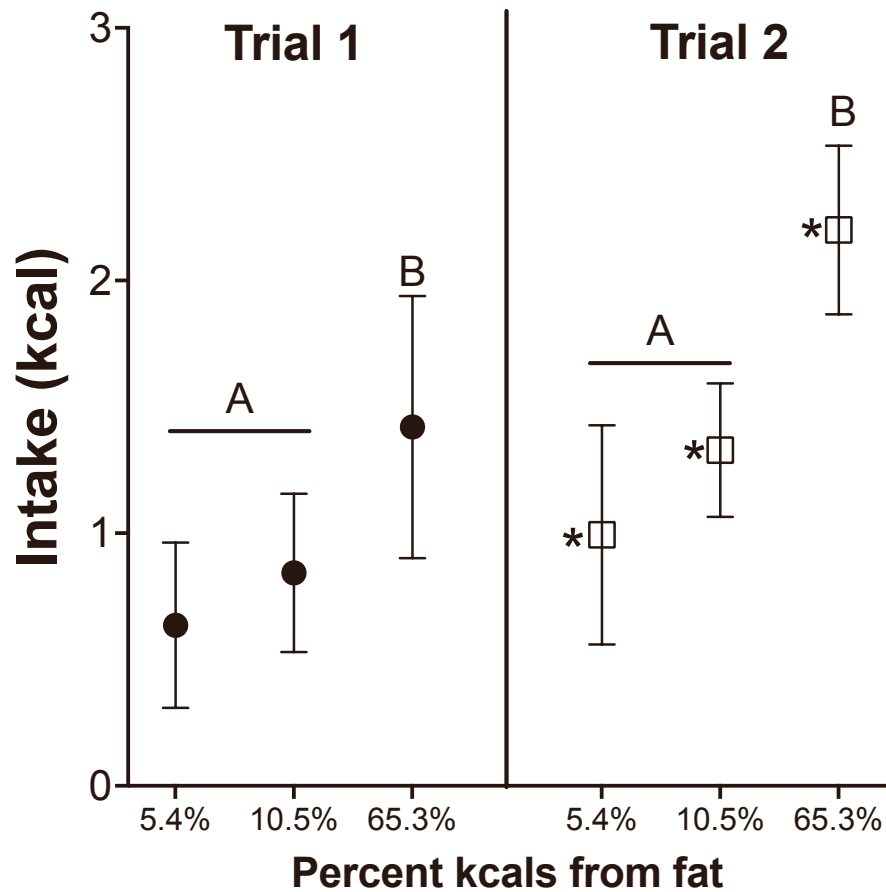
**Supplemental Figure 2. Non-nutritive sweetener increases water intake, Related to Figure 1.**

Mice were offered sweetened or unsweetened water for six days, and intake was measured daily. Data are displayed as mean  $\pm$  standard deviation. \*  $p < 0.05$  using a student's T test to compare intake of the sweetened group to intake of water.  $n = 3$ / group. Data support results in Fig 1.



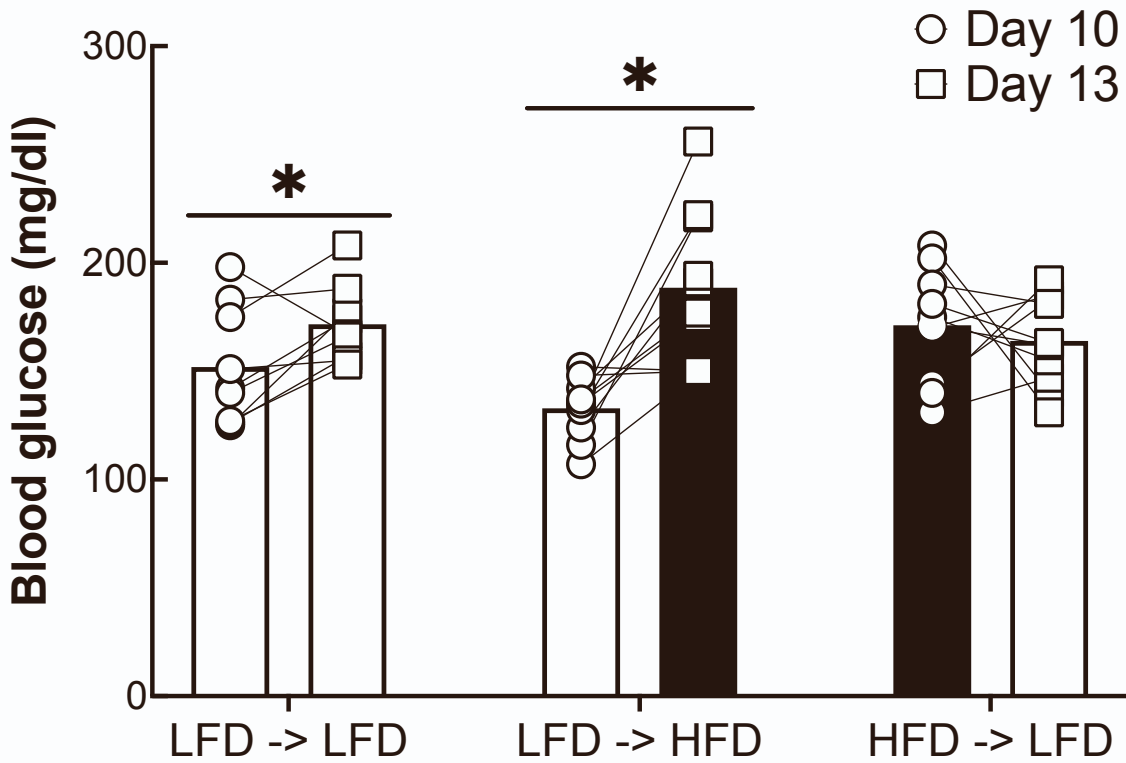
**Supplemental Figure 3. Daily food intake and body weight of mice, Related to Figures 3**

Data are from mice shown in Figures 3A & 3B presented as mean  $\pm$  standard deviation which is marked by the shaded regions. n=5/group.



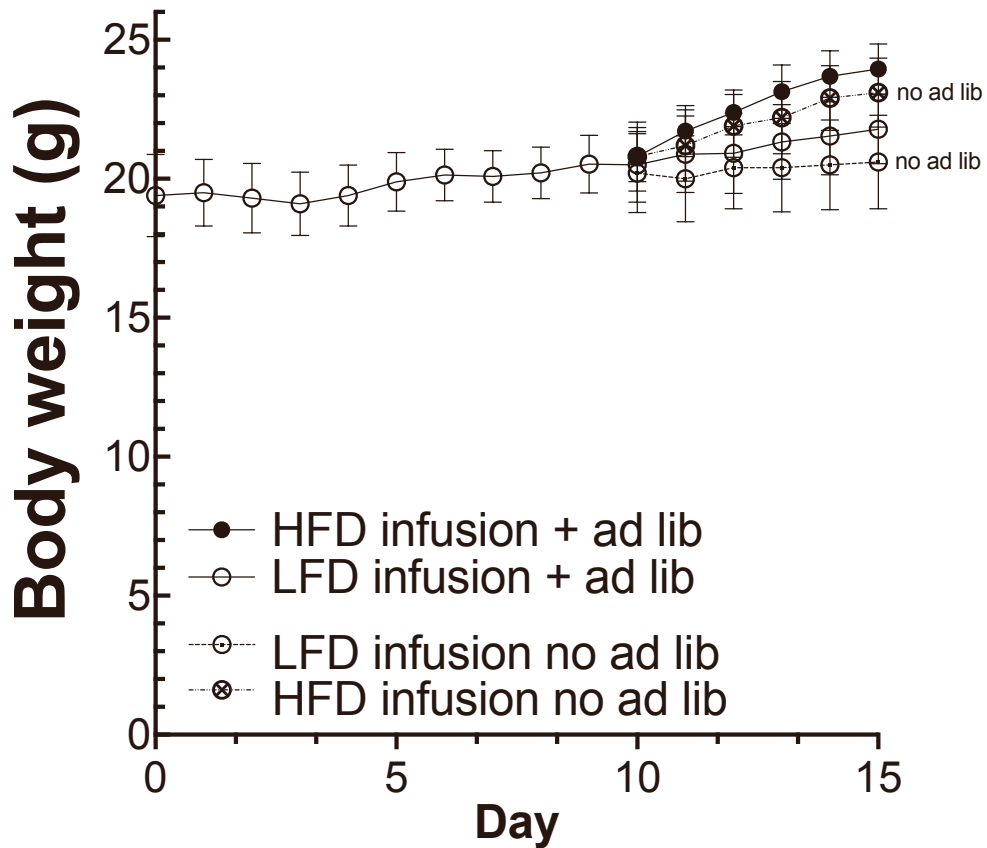
**Supplemental Figure 4. Short access test show that both acute and learned aspects of the diet influence intake, Related to Figure 3**

15 mice were offered diets of differing fat content in a random order. After the first introduction (Trial 1), the series was repeated (Trial 2). Different letters represent significant differences within a trial ( $p < 0.05$  ANOVA with post hoc T test with Benjamini Hochberg correction). \*  $p < 0.05$  comparing trial 1 to trial 2 of the same diet using a paired T-test. Diet introduction order was not a significant factor affecting intake (ANOVA).



**Supplemental Figure 5. Blood glucose is higher during HFD infusion than during LFD infusion, Related to Figure 5**

Data are from the experiment shown in 4D. n=9-10/ group and each open shape represents an individual data point. \* p<0.05 using a paired T test. Transparent bar represents average intake during LFD infusion and black bar represents average intake during HFD infusion.



**Supplemental Figure 6. Intragastric infusion of the high fat diet induces weight, Related to Figure 5.**

In addition to the groups shown in figure 5A-D, two other groups were infused but not offered ad lib to confirm that sufficient calories were infused into the mice. Data are displayed as mean  $\pm$  standard deviation; n= 5-6/ group.

Experiment	Diet	Additives	Caloric Density	Macronutrient Content
<p>Sucralose and sucrose preference testing</p> <p>Figure: 1A-F; 6 F-G</p>	Natrel Fine Filtered 2% milk	Sucralose (Sigma Aldrich, 69293-100G), Sucrose (Sigma Aldrich, 573113-5KG)	0.5416 kcals/mL	<p><b>Natrel 2% milk:</b> 34.9% kcals fat, 27.9% kcals protein, 37.2% kcals carb</p> <p><b>Natrel 2% milk with 30% kcal from sucrose:</b> 24.4% kcals fat, 19.5% kcals protein, 56.1% carb (30% kcals sucrose)</p>
<p>Initial high-fat and low-fat preference testing with sweeteners, ad lib diets during overfeeding, and diets for first post-ingestive effects experiment</p> <p>Figures: 1 G; 2; 3 A-D; 5 E-G; 6 A-E; Supplemental 3; 4</p>	<p>Village Farm Instant non-fat milk Powder, Land O'Lakes Half and Half</p> <p>Half and Half and Skim milk powders Combined in different amounts to create diets with 10% or 60% kcal from fat</p>	Sucralose and sucrose (Sigma Aldrich)	1kcal/mL	<p><b>5% kcal fat:</b> 5.4% kcals fat, 40.7% kcals protein, 53.9% kcals carb</p> <p><b>10% kcal from fat: LFD above</b></p> <p><b>20% kcal from fat:</b> 20.8% kcals fat, 34% kcals protein, 45.2% kcals carb</p> <p><b>40% kcal from fat:</b> 42.3% kcals fat, 24.7% kcals protein, 33% kcals carb</p> <p><b>60% kcal from fat: HFD above</b></p>
Post-ingestive effects of a HFD	Similac Alimentum		1kcal/mL	<b>LFD:</b> 10% kcals from fat,



(infusion and ad-lib diets)  Figures: 2H; 5A-D; Supplemental 6	(Abbott Nutrition), and Maltodextrin (Sigma Aldrich, 419699)			2.5% kcals protein, 87.5% kcals carbs  <b>HFD:</b> 50% kcals from fat, 11% kcals protein, 39% kcals carb
Protein matched diets using half and half as fat source  Figures: 3E; 4A-C	Land O'Lakes Half and Half, Whey Protein Powder (GNC Pro Performance® 100% Whey, 369951), Maltodextrin (Sigma Aldrich, 419699)	AIN 93 vitamin mix (DYETS #310025)	1kcal/ ml	<b>LFD:</b> 10% kcals from fat, 10% kcals protein, 80% kcals carb  <b>HFD:</b> 60% kcals fat, 10% kcals protein, 30% kcals carb
Protein matched diets using Intralipid as the fat source  Figure 2G; 4D-G	Whey Protein Powder (GNC Pro Performance® 100% Whey, 369951), Intralipid (Sigma Aldrich, I141-100ML), Maltodextrin (Sigma Aldrich, 419699)	AIN 93 vitamin mix (DYETS, 310025)	1kcal/mL	<b>LFD:</b> 10% kcals from fat, 10% kcals protein, 80% kcals carb  <b>HFD:</b> 60% kcals fat, 10% kcals protein, 30% kcals carb
Mineral Oil Diet  Figure 3E	Land O'Lakes Half and Half, Whey Protein Powder (GNC Pro Performance® 100% Whey, 369951), Maltodextrin (Sigma Aldrich,	AIN 93 vitamin mix (DYETS #310025)	1kcal/ ml	<b>LFD:</b> 10% kcals from fat, 10% kcals protein, 80% kcals carb + 28.2g mineral oil/ 1L diet

	419699), Mineral oil (Walgreen's, NDC 0363- 0831-43)			
Experiment 4. Overfeeding Infusion  Figure 6	Ensure Original Vanilla Powder		<b>0.875kcal/mL</b>	32.4% kcals fat, 14.4% kcals protein, 54.2% kcals carb
Surgery recovery diet	PicoLab rodent diet 20 #5053		3.07 kcal/g	13.205% kcals fat, 24.651% kcals protein, 62.144% kcals carb

**Supplemental Table 1. Diets and composition.**

This table shows all diets and their macronutrients used in the different experiments. This table is part of the STAR methods.