The impact of obesity on ingestion-induced hippocampal *Arc* expression in male rats

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Introduction

Obesity is a chronic disease that affects more than 33% of all American adults[1] and roughly 13% of all adults worldwide[2]. Obesity brings numerous complications such as cardiovascular diseases, type II diabetes, and arthritis, and impairs many organs such as the heart, pancreas, and liver. In addition to the peripheral impacts of obesity, obesity also influences brain function. In particular, obesity and overeating impair hippocampal function, which is vital for memory formation. In humans impairing memory of a meal increases subsequent intake. Our evidence suggests that hippocampal neurons form a memory of a meal and inhibit eating during the period after a meal. For example, we have shown that ingesting a sucrose meal activates molecules necessary for hippocampal memory formation, such as activity regulated cytoskeleton associated protein (*Arc*) and that inhibiting hippocampal neurons after eating a sucrose meal causes animals to eat sooner and eat more. Obesity and overeating impair biochemical processes in the hippocampus required to form memories and we hypothesize that obesity disrupts hippocampal formation of a memory of a meal which could further contribute to obesity. The objective of this study is to test the prediction that feeding rats a high-fat diet resulting in obesity impairs sucrose ingestion-induced *Arc* mRNA expression.
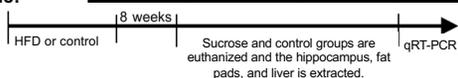
Methods

Subjects: Adult male Sprague-Dawley rats (N= 48)
Diet: High fat diet (HFD): lard, standard chow, and water *ad libitum* OR control diet: chow and water. Food intake and body mass are measured regularly.
Rats that gain the most weight during the first week (highest tertile) will be categorized as Lard-obese and those that gain the least weight (lowest tertile) will be categorized as Lard-lean.
After 8 weeks, rats will be provided with either a solution of 32% sucrose for 10 min for 3 consecutive days (Sucrose) or given comparable handling (Cage-control).
On the third day of sucrose consumption, rats will be anesthetized (isoflurane 5%) and decapitated 10 min after they were given sucrose, and the hippocampi will be extracted. To confirm obesity, fat pads (inguinal, epididymal and retroperitoneal) and liver will be collected and weighed.
Arc mRNA expression will be measuring using quantitative real-time polymerase chain reaction.

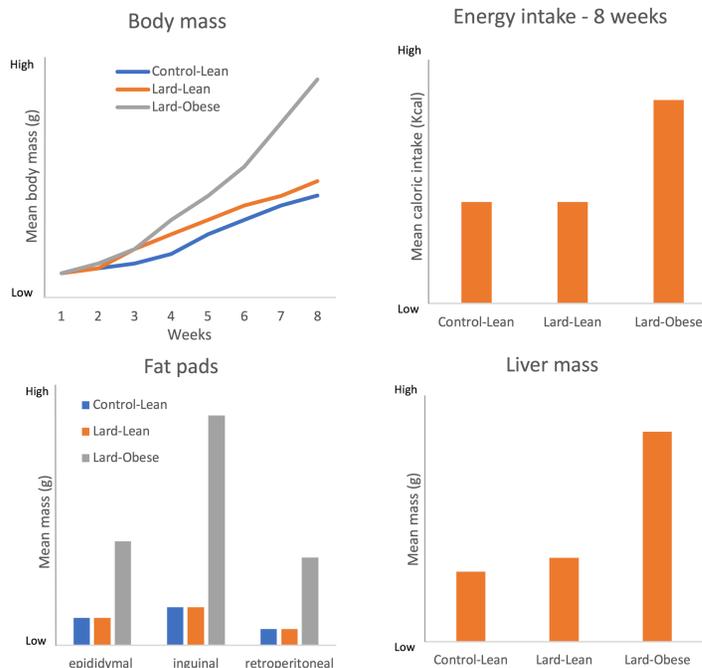|		Control	Lard-Lean	Lard-Obese
Experimental design:	**Cage-control**	n=6	n=6	n=6
	Sucrose	n=6	n=6	n=6

Experiment timeline:

HFD or control — 8 weeks — Sucrose and control groups are euthanized and the hippocampus, fat pads, and liver is extracted. — qRT-PCR

Predicted Results

Physiology

Body mass — Control-Lean, Lard-Lean, Lard-Obese; Mean body mass (g); Weeks 1–8

Energy intake - 8 weeks — Mean caloric intake (Kcal); Control-Lean, Lard-Lean, Lard-Obese

Fat pads — Control-Lean, Lard-Lean, Lard-Obese; Mean mass (g); epididymal, inguinal, retroperitoneal

Liver mass — Mean mass (g); Control-Lean, Lard-Lean, Lard-Obese

Sucrose ingestion and Arc expression

Sucrose intake — Mean sucrose consumed (g); Control-Lean, Lard-Lean, Lard-Obese

Arc mRNA expression — Mean fold change relative to cage-control; Control-Lean, Lard-Lean, Lard-Obese
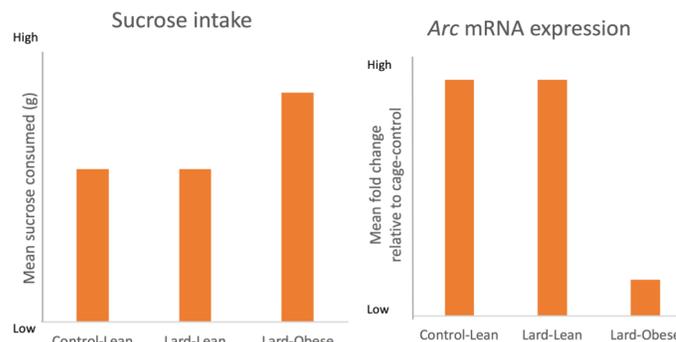
Discussion

If the predicted results indicate increased sucrose intake and reduced *Arc* mRNA expression in lard-obese rats relative to the lard-lean and control-lean groups, then this would be consistent with the hypothesis that obesity disrupts hippocampal formation of a memory of a meal. It is possible that obesity could impact *Arc* in the absence of sucrose (i.e., cage-control).

To further test the hypothesis, future studies could conduct a similar experiment to measure other proteins critical for memory formation, such as brain-derived neurotrophic factor (BDNF) or phosphorylation of cAMP responsive element binding protein (CREB).

Another way to test the hypothesis that obesity impairs hippocampal *Arc* would be to repeat the experiment then determine the effects of inhibitory avoidance training on *Arc* in obese vs. lean rats.

To determine whether impaired Arc caused obesity or whether obesity impaired Arc, future studies could test for Arc mRNA expression in rats during the first week before they become obese.[3]

An alternative may be to knockout the genes involved in *Arc* expression and test for whether or not they become obese.

Acknowledgments

References

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