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 adults1 and roughly 13% of all adults worldwide2. 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.

Experimental design:

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Lard-Lean</th>
<th>Lard-Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cage-control</td>
<td>n=6</td>
<td>n=6</td>
<td>n=6</td>
</tr>
<tr>
<td>Sucrose</td>
<td>n=6</td>
<td>n=6</td>
<td>n=6</td>
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</tbody>
</table>

Experiment timeline:

<table>
<thead>
<tr>
<th></th>
<th>HFD or control</th>
<th>Sucrose and control groups are euthanized and the hippocampus, fat pads, and liver is extracted.</th>
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</thead>
<tbody>
<tr>
<td>8 weeks</td>
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Predicted Results

Physiology

- Body mass
- Energy intake - 8 weeks
- Fat pads
- Liver mass

Sucrose ingestion and Arc expression

- Sucrose intake
- Arc mRNA expression

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.

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

Acknowledgments
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References