REPLY TO PEIRETTI ET AL.:

Effect of CAGE on fat uptake and food intake

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We thank Peiretti et al. (1) for their interest in our work (2) and for the suggestions for follow-up research. Peiretti et al. (1) ask about the role of reduced food consumption in the observed effect on reduced weight gain. We respectfully acknowledge this question.

In our work (2), the effect of choline and geranate (CAGE) on fat uptake is hypothesized to occur primarily through a physical phenomenon. Specifically, the amphiphilic nature of CAGE enables its interactions with the lipophilic fat molecules (3), and forms self-assembled structures that are large in size. The large size of the resultant droplets is hypothesized to be responsible for reduced uptake across the intestine, which was demonstrated using docosahexaenoic acid (DHA) as a model fat molecule. This hypothesis was inspired by our earlier observation that CAGE, while an enhancer of transport for peptides and hydrophilic drugs, reduces the transport of hydrophobic molecules in a dose-dependent manner (4). Based on these two observations, it appears that CAGE has an effect of reducing the transport of certain hydrophobic molecules across the intestine. Experiments performed with DHA show increased retention in the intestine and reduced absorption in the blood.

Peiretti et al. (1) propose an interesting experiment with pair-fed controls to dissociate the contributions of food intake and fat uptake. We will incorporate this suggestion in our future studies. As an additional point of note, as mentioned in our publication, CAGE also exhibits DPP-IV inhibition activity. In addition to reduced food intake, DPP-IV inhibition has an effect on glucagon-dependent insulin secretion, stomach emptying, and postprandial glucagon (5–7). Some of these effects, especially insulin secretion and postprandial glucagon secretion, are significantly dependent on the pathological status, for example, obesity or type 2 diabetes. Collectively, as pointed out in our publication (2), the therapeutic effect of CAGE could arise from a combination of multiple effects, including the physical effects of gastrointestinal fat retention, reduced food intake, and biological mechanisms associated with DPP-IV inhibition which may potentially involve leptin signaling. We acknowledge these multiple possibilities and possible explanations for the observed effects, and look forward to understanding them better through further experiments. In the meantime, we thank Peiretti et al. for the interest, enthusiasm about the therapeutic possibilities, and excellent considerations for future experiments.

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