

# Is ionic choline and geranate (CAGE) liquid caging diet-derived fat, limiting its absorption?

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A recent interesting study from Nurunnabi et al. (1) demonstrates that, in vitro, an ionic liquid consisting of choline and geranate (CAGE) generates large lipid microparticles, when coincubated with the model lipid molecule docosahexaenoic acid (DHA). Upon application of these preformed CAGE-DHA microparticles to rat intestines ex vivo or orally to starved rats in vivo, absorption of DHA was largely inhibited when compared with noncomplexed DHA. In the more physiological part of this study, high-fat diet-fed rats were treated with CAGE (without DHA) applied in oral capsules or left untreated and followed for 30 d. Rats treated with a high dose of CAGE displayed reductions in both weight gain and food intake, without any apparent side effect.

The in vivo data, crucial to the physiological relevance of this study, are claimed to support the hypothesis that CAGE cages fat from food, reducing its absorption by the gastrointestinal (GI) tract. However, proof for this claim is lacking. First, there is no evidence that CAGE is caging fat derived from food. While CAGE complexes DHA in a mixture exclusively consisting of CAGE and DHA in vitro, it is uncertain whether lipid microparticles form when CAGE meets complex combinations of food components. Second, if CAGE reduces absorption of diet-derived fat from the GI tract, the fat content of stool should be significantly increased, similarly to what has been demonstrated for orlistat-treated rats and humans (2, 3). The authors have stated that this is likely the case, but have not investigated this (1). Third, administration of the

10- $\mu$ L CAGE capsules reduced weight gain by 12% and food intake by 20%. These two effects seemed to be closely linked, since the 5- $\mu$ L CAGE dose did not affect weight gain, while marginally reducing food intake by only 5%. Is it possible that the reduction in weight gain in high-dose CAGE rats is exclusively due to the reduced food intake? To investigate whether CAGE reduces weight gain irrespective of any effect on food intake, control rats should have been "pair-fed," that is, receiving the same amount of food as was consumed by the rats receiving the 10- $\mu$ L CAGE dose (4–6). If no further reduction in weight gain had been observed in CAGE-treated rats compared with the pair-fed controls, this would provide evidence against the authors' main hypothesis that CAGE administration in vivo reduces fat absorption and, consequently, weight gain.

Taken together, from our point of view, it is not clear what happens when CAGE is administered in vivo; whether CAGE interacts with lipids postprandially, preventing them from absorption; and what underlies the reduction in weight gain. Nevertheless, the CAGE-induced limitation of weight gain is interesting for obesity treatment and warrants further investigation. Moreover, if side effects are also absent during longer treatments, CAGE may be a promising future alternative to current weight loss drugs, such as orlistat and lorcaserin, which are known to be associated with several serious adverse effects (3, 7), and to more invasive methods involving bariatric surgery (8).

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The authors declare no competing interest.

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