Opinion

Micelle sequestration polymers

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Obesity is a major problem in the United States. The cause of obesity is mainly due to caloric imbalance. The authors of this journal article, Jian Qian and Bradley P. Sullivan from the Department of Chemistry at The University of Kansas, and Cory Berkl and from the Department of Chemical and Petroleum Engineering, also at The University of Kansas. They proposed in their article, "pH-Responsive Micelle Sequestrant Polymers Inhibit Fat Absorption" written in the American Chemical Society's *Biomacromolecules* a safer alternative to other anti-obesity drugs. The goal is to have more caloric balance by getting rid of lipids from foods that were eaten. Lipids are high in calories, equaling 9 calories per gram, according to the Atwater Factor.

Lipids are what fats and triglycerides are derived from. The two ways that lipids are absorbed in the small intestine are by emulsification and lipolysis. During emulsification, lipids are broken down into micelles, which are smaller versions of lipids by bile acids. Bile acids also hold micelles in suspension. Bile acids are made by the liver and are stored in the gallbladder until they are motivated to be released into the small intestine. Bile acids are detergent-like particles made in the body from cholesterol. After emulsification, lipolysis occurs. Triglycerides, which are the main dietary lipids, are digested by the enzyme pancreatic lipase, which brings forth monoglycerides and free fatty acids. Both of them can go into enterocytes or diffuse. Lipolysis is important because when large fat molecules break down into micelles that provide more surface area of newly developed triglycerides to meet up with enzyme pancreatic lipase and break. However, if emulsification is disrupted, triglycerides cannot be broken down by pancreatic lipase well enough. Therefore, in the end, fat cannot be absorbed well enough in the gastrointestinal tract.

The gastrointestinal tract undergoes significant pH changes. When bolus enters the stomach, it goes into the stomach very acidic environment, which is at a pH of <5.0. Then, it goes into the duodenum, which is less acidic than the stomach's environment (pH <6.0). Then, it heads over to the jejunum and ileum, where the pH is neutral there (pH ~6.0).

The authors' goal was to create micelle sequestrant polymers (MSPs), orally acting drugs that can target dietary lipid absorption that does the following: respond to changing pH in the gastrointestinal tract bind up, and inhibit lipid absorption in the GI tract via pH-triggered "flocculation process."

The proposed mechanism for MSPs is as follows:

a. MSPs are made soluble and mixed with chyme in the stomach.

b. MSPs are mixed with chyme, which goes into the duodenum, making the gallbladder contract and release bile acids into the duodenum, which leads to bile acids and fats emulsifying to make micelles, which are negatively charged.

c. MSPs (which have a net positive charge) bind micelles by way of electrostatic interactions. During then, the pH increases to ~6.0 in the jejunum.

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d. MSPs, within the ileum, gather together to form MSP-micelle complexes which are stable and flagellate out of suspension.

e. MSP-micelle complex go through the colon.

f. MSP-micelle complex go through feces.

The authors had criteria by which MSPs were designed:

i. They can act locally in the GI tract.

ii. Cationic enough to interact with lipid micelles, which are negatively charged.

iii. Has to be soluble in the stomach, plus it has to be insoluble in an environment like the ileum. In other words, MSPs must be able to respond well to those pH changes.

The authors engineered MSPs into two types: poly (2-(diisopropylamino) ethyl methacrylate (PDPA), which has a pH of 6.5, and poly(2-(dibutylamino) ethyl methacrylate (PDBA), which has a pH of 5.5. The authors stated that they have never been used before as pharmaceutical agents taken by mouth used in order to bind up fats and to motivate bile acids to be released. The authors assessed the following: size, composition, pH sensitivity, and bile acid and triglyceride binding capacity in an *in vitro* model and an *in vivo* model.

In the *in vitro* model, bile acids sequestration was studied. Four bile acids found in most of human bile were added to fed-state-simulated intestinal fluid (FeSSIF), gone through process to see how much of the bile acids were sequestered. Fat sequestration was also studied *in vitro*. Micelles containing lipid mixed with FeSSIF that has bile to see how much fat is sequestered.

In the *in vivo* model, 6 male mice between the ages 8-12 weeks were fed a high-fat diet (45% kcal from fat, 30% kcal from sucrose) ad libitum. For the experiment, the following were solubilized in water and mixed homogeneously mixed with high-fat diet powder: MSPs, the FDA-approved controls cholestyramine and Welchol (both are ion exchange resins), plus high-fiber substances inulin and chitosan, plus water. Each mouse was put in an individual metabolic cage and fed this experimental mix for 3 days ad libitum. Feces from each mouse was collected and the bile acid and triglyceride contents were collected and evaluated.

The authors determined that MSP performance is better *in vitro* than *in vivo* due to other molecules in the body (i.e. negatively charged

glycoproteins found in the GI tract mucus interact electrostatically with MSPs, making them less likely to sequester anything. Plus, the authors suggest that either MSPs may cause "differential micellar formation" in the small bowel after bile acids exit the body via feces or "may have differential association with large triglyceride droplets in the stomach."

The authors concluded that MSPs could possibly be further developed to prevent the body from taking in too many calories from fat via micelle sequestration. However, more studies should be done to fully understand how MSPs work in the body. Also, MSPs could also be used to improve the removal of toxins or other molecules secreted in bile and help improve blood flow between the hepatic system and GI system with its pH-sensitivity qualities. MSPs are soluble in acidic environments but are insoluble in a neutral and basic climate MSPs could react to pH changes in the GI tract. *In vitro*, MSPs could react to pH changes in the GI tract rapidly. *In vivo*, MSPs taken orally enhanced significantly triglycerides and bile acids via feces. In fact, MSPs did this 9-10 times better in comparison to the control. Furthermore, the authors suggest that MSPs may be a safe way to treat and/or prevent obesity due to a high-fat diet, as well as treat and/or prevent weight gain, and lower the risks of cardiovascular disease. MSPs are able to bind, sequester and eliminate whole micelles in the small bowel. Finally, MSPs could serve as a possible hypercholesterolemia medication, since high cholesterol is a comorbidity frequently seen in obese patients.

Since this is a recent study, they have been no recent follow-ups on it. However, the study of MSPs has been reported in various media in the United States and the United Kingdom, such as *Consumer Affairs* and *The Mirror*. From a perspective as a nutrition professional, more research should be done to make sure that MSPs are truly a safe alternative to controlling obesity and preventing excess fat absorption. Eating a more calorically balanced diet and exercising adequately should be the first thing to do before taking any medication. Also, more doctors should be aware of this potential drug and request more research for it.

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Conflict of interest

The author declares no conflict of interest.