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α-Cyclodextrin as a food ingredient to reduce fat absorption

KEYWORDS: Obesity, dietary fat, α-cyclodextrins, fat absorption.

Abstract New approaches are needed to reduce the prevalence of obesity. One approach for limiting weight gain or facilitating weight loss may be to use food ingredients that reduce the absorption of dietary fat. One such ingredient may be alpha-cyclodextrin (α-CD), which has been shown to bind fat *in vitro*. Although animal studies have been inconsistent in demonstrating a reduction in body weight with α-CD feeding, a clinical trial found that α-CD halted weight gain in obese diabetics. Further, animal studies support a reduction in fat absorption with α-cd feeding. Thus, α-CD shows promise as a food ingredient to reduce fat absorption and warrants further study in this regard.

INTRODUCTION

The incidence of obesity has reached historically unprecedented levels. Within the United States, approximately 75% of adults are either overweight or obese (1). Although the proportion of overweight or obese individuals is less in Western Europe, it is still very high at approximately 61% in men and 48% in women (2). Considerable evidence demonstrates that being overweight or obese increases the risk for a number of chronic diseases, including type 2 diabetes, cardiovascular disease, hypertension, and certain cancers (3). The medical costs associated with treatment of obesity-related diseases is enormous, with projected increases of $48-66 billion per year in the USA and £1.9-2 billion per year in the UK (4). Thus, the high incidence of obesity represents a major public health issue.

Pharmacological approaches to reducing obesity have been only modestly successful and can present serious side effects. Thus, different approaches to reducing obesity remain urgently needed. One such approach would be to develop food ingredients that would aid in limiting weight gain or achieving weight loss. One strategy is to formulate food products in which the digestible food components are incompletely absorbed. The use of caprenin, a synthetic fat which contains fatty acids that are incompletely absorbed, in candy bars is an example of one such attempt, albeit a commercially unsuccessful one.

CYCLODEXTRINS AS FAT-BINDING AGENTS

Another approach is to limit fat absorption by the use of a food ingredient that would bind fat or fat digestion products and prevent their absorption. Alpha-cyclodextrin (α-CD) may be one such food ingredient. Cyclodextrins are oligosaccharides that are formed from the hydrolysis and cyclization of starch by the action of cyclodextrin glycosyltransferase (5). They consist of either six, seven, or eight glucopyranose units linked together to form α-, β-, or γ-cyclodextrin, respectively. The structure of α-CD is shown in Figure 1. The cyclodextrins have a toroidal ring structure with the hydroxyl groups on the edge of the ring and the apolar C_3 and C_5 hydrogens and ether-like oxygens oriented towards the inside, resulting in a molecule that is water-soluble but with a hydrophobic cavity (6, 7), as shown in Figure 2. This allows cyclodextrins to host hydrophobic molecules, forming an inclusion complex, a so-called 'host-guest' reaction. Of the cyclodextrins, α-cyclodextrin (α-CD) has a particular affinity for binding fatty acids, with a greater preference for saturated fatty acids relative to unsaturated fatty acids (8, 9). Affinity for binding also varies by esterification state; non-esterified fatty acids show the greatest affinity, with affinity declining as the number of fatty acids esterified to glycerol increases (8, 9). α-CD, but not β- or γ–cyclodextrin, has been shown to bind cholesterol (10).
This ability of α-CD to bind fatty acids suggests it would be a candidate for a food component to decrease absorption of dietary fat. However, only if it remained intact through the small intestine, the site of fat absorption, would it be effective. The finding that, *in vitro*, α-CD resists digestion by salivary and pancreatic amylases (11, 12) indicates that α-CD has the characteristics of a dietary fiber and, thus, will survive passage through the small intestine undigested.

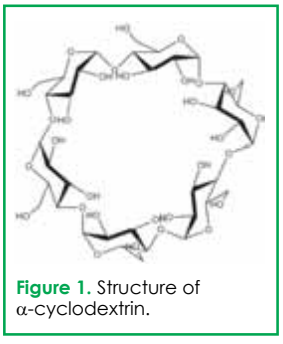
Figure 1. Structure of α-cyclodextrin.

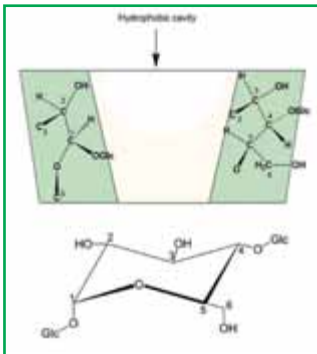

Figure 2. Toroidal structure of α-cyclodextrin, indicating its hydrophobic cavity. Adapted from (7).

EFFECT ON BODY WEIGHT AND BODY FAT

Given that α-CD is a dietary fiber that specifically binds lipids *in vitro*, the question is whether it will bind lipids *in vivo*, and to a degree sufficient to have a biological effect on a host animal, such as reducing body weight or slowing weight gain, or reducing body fat. Several studies have examined the effect of α-CD on body weight and body fat in animal models. Suzuki and Sata fed diets varying in the concentrations of α-CD to rats for up to 110 days (13). Weight gain of rats fed diets containing 19.5% or 39% α-CD was not significantly different from the α-CD-free control diet. Rats fed either 58.5% or 78% α-CD did experience significantly less weight gain. Further, in the rats fed the 39% α-CD-containing diets, there was a reduction in fat pad weight, a measure of whole body adiposity, and there was a trend toward lower fat pad weight in rats fed the 19.5% α-CD-containing diet. However, in this study, the authors substituted α-CD for corn starch. Consequently, in the diets containing the highest concentration of α-CD there was little corn starch, and very little fat, such that the caloric density of these diets was extremely low. It is most likely that the reduced weight gain in rats fed the highest dietary concentration of α-CD was simply due to the low caloric density of the diets, not to the α-CD per se. Further, the reduction in fat pad weights also may have been due to the lower caloric density of the diets. In another study, using a dietary concentration of 5% α-CD, rats fed for 7 days did not differ in body weight gain from the α-CD-free control diet (14). However, a 7 day feeding trial is rather short to detect differences in body weight due to a dietary intervention, so the lack of an effect would not be unexpected. Artiss et al. fed rats diets containing 4% α-CD for 6 weeks, using both low fat and high fat background diets (15). Although α-CD had no effect on weight gain when fed as part of a low fat diet, when included in a high fat diet, weight gain was significantly reduced by 7.4% relative to a high fat diet without α-CD. Inclusion of α-CD in the high fat diet also tended to reduce body fat relative to the high fat diet without α-CD (p=0.11). Again, α-CD had no effect on body fat when fed as a part of the low fat diet. In a subsequent study by the same group, the effect of α-CD on body weight was examined in LDL receptor (LDLr) knockout mice (16). The mice were fed moderately high fat diets (21% by wt.) for 14 weeks, containing either 2.1% α-CD or no α-CD. Weight gain, however, did not differ between the two groups at the end of the trial. Thus, animal studies examining the effect of α-CD on body weight and body fat are inconsistent. It appears that with a background diet very low in fat, α-CD has no effect on body weight at levels in the diet that might be achievable by humans. Whether α-CD might reduce body weight and body fat in the context of a high fat diet warrants further investigation.
In the single clinical trial of α-CD conducted to date, obese type 2 diabetic subjects took 6 g of α-CD per day (two 1-g capsules with each meal) for 3 months (17). At the end of the trial, subjects taking α-CD gained no weight over the 3 month trial period, whereas subjects consuming the placebo gained a statistically significant amount of weight. The BMI showed the same pattern; subjects taking α-CD had no change in their BMI whereas subjects taking the placebo experienced a significant increase in their BMI. This study suggest that, at least in obese diabetics, consumption of α-CD can limit weight gain.

EFFECT ON FAT EXCRETION

If α-CD can in fact lead to weight loss, or at least slow weight gain, as both the clinical trial and at least one animal trial suggests, is the mechanism due to decreased fat absorption as a result of fat binding by α-CD? Artiss et al. (15) examined this question in their study of rats fed α-CD incorporated into the diet at 10% of the dietary concentration of the fat. Fecal excretion of fat from animals fed the high fat diet did not differ between the control and α-CD-containing (4% by wt.) diet. However, the percentage of fat in the feces was significantly greater in the rats fed the α-CD compared to the control group. Although one might consider this as evidence of decreased fat absorption due to α-CD, this result must be viewed with caution. First, the authors' method of fat extraction from the feces gives an incomplete extraction, as it is necessary to acid hydrolyze the sample prior to solvent extraction to achieve a complete fat extraction (Gallaher et al., personal observation). Second, α-CD is highly fermented in the large intestine (12). This leads to the disappearance of the α-CD, and the expansion of the large intestinal microflora population. Since bacterial lipids may account for one-half to three-quarters of fecal lipids (18), the increase in fecal lipid concentration may well be due to the increase in bacterial lipids due to fermentation of the α-CD. Recently, a study in dogs examined the question of whether α-CD would reduce intestinal fat absorption by determining the effect of α-CD on total digestive tract fat digestibility (19). In this study, dogs were administered α-CD orally immediately after feeding, in amounts of either 6 or 12 g/d. Control animals received only water. There was a significant and linear decrease in acid-hydrolyzed fat digestibility with increasing α-CD, a finding consistent with the concept of a reduction in fat absorption by α-CD.
The challenge with any method examining changes in fat absorption by measurement of fecal fat excretion is the high concentration of bacterial lipids present in the feces, which can make it difficult to detect small differences in fat absorption. Gallaher et al. (20) circumvented this issue by incorporating radiolabeled triacylglycerols into the diet to distinguish dietary lipids from fecal bacterial lipids. In this study, rats were fed diets containing either 5% cellulose as a control (CEL), 5% α-CD added directly to the diet (ACD), or 5% α-CD in which the dietary fat (including the radiolabels) were complexed to α-CD prior to addition to the diet (CpxACD). Both ^{14}C-triolein and ^{3}H-tripalmitin were used to determine whether excretion of saturated fats was favored over unsaturated fats, given that, *in vitro*, α-CD preferentially binds saturated fat (8, 9). Although excretion of ^{14}C-triolein did not differ between rats fed the CEL diet and the ACD diet, ^{3}H-tripalmitin excretion was increased 7-fold in the ACD diet compared to the CEL diet. Rats fed CpxACD had significantly increased ^{14}C-triolein excretion relative to the CEL diet; however, ^{3}H-tripalmitin excretion was dramatically increased by 16-fold relative to the CEL diet. Thus, these findings, using a more sensitive and specific approach to determining changes in intestinal fat absorption than fecal fat excretion, suggest that α-CD does bind dietary fat and reduces its intestinal absorption, preferentially binding saturated fats.

CONCLUSIONS

Thus, the results from animal studies do, on balance, support the concept that α-CD reduces intestinal absorption of dietary fat. Additionally, the lack of weight gain in subjects taking α-CD in the single clinical trial to date suggests that the reduction in fat absorption produced by α-CD may be sufficient to impart a physiological benefit. Further studies of the potential for α-CD as an aid in maintaining or achieving a healthy body weight are warranted.

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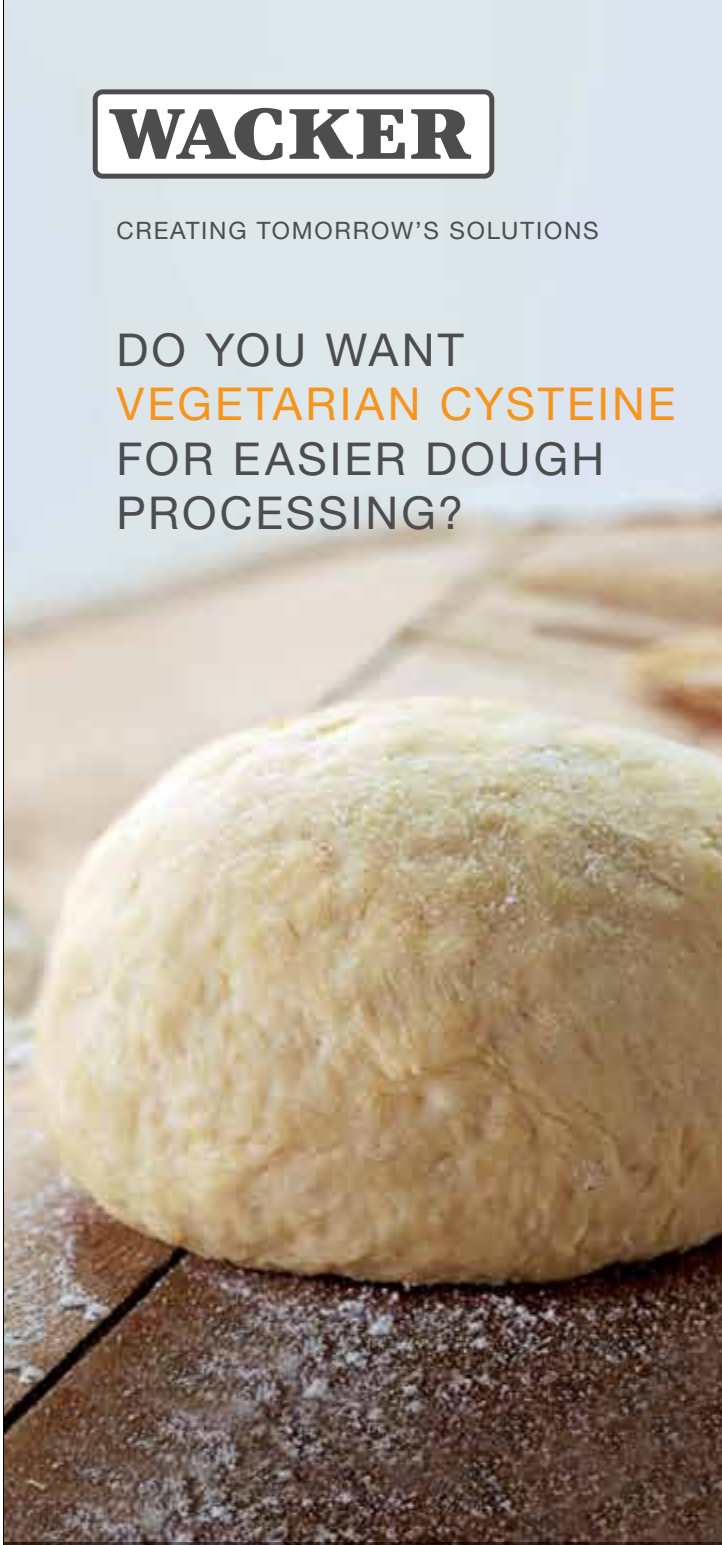

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