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Effects of 2-week ingestion of (−)-hydroxycitrate and (−)-hydroxycitrate combined with medium-chain triglycerides on satiety and food intake

E.M.R. Kovacs*, M.S. Westerterp-Plantenga, M. de Vries, F. Brouns, W.H.M. Saris

Department of Human Biology, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands

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Abstract

The aim of this study was to assess the effects of 2 weeks of supplementation with (−)-hydroxycitrate (HCA) and HCA combined with medium-chain triglycerides (MCT) on satiety and energy intake. The experimental design consisted of three intervention periods of 2 weeks separated by washout periods of 2 or 6 weeks in a double-blind, placebo-controlled, randomized, and crossover design. Seven male and 14 female normal to moderately obese subjects (mean ± S.D.; age, 43 ± 10 years; body mass index, 27.6 ± 2.0 kg/m^2) participated in this study. Subjects consumed three self-selected meals and four isoenergetic snacks daily with either no supplementation (PLA), with 500 mg HCA (HCA), or 500 mg HCA and 3 g MCT (HCA + MCT). Each intervention period ended with a test day, consisting of a standardized breakfast and ad libitum a lunch and a dinner. There was a significant body weight (BW) loss during the 2 weeks of intervention (PLA, −0.5 ± 0.3 kg, $P < .05$; HCA, −0.4 ± 0.2 kg, $P < .05$; HCA + MCT, −0.7 ± 0.2 kg, $P < .01$), but this reduction was not different between treatments. Twenty-four-hour energy intake (PLA, 8.1 ± 0.3 MJ; HCA, 8.3 ± 0.3 MJ; HCA + MCT, 8.4 ± 0.3 MJ) and the area under the curve of the appetite-related parameters during the test day were similar for all treatments. Two weeks of supplementation with HCA and HCA combined with MCT did not result in increased satiety or decreased energy intake compared to placebo in subjects losing BW.

Keywords: (−)-Hydroxycitrate; Medium-chain triglycerides; Appetite; Satiety; Energy intake; Body weight loss

1. Introduction

The increasing incidence of obesity is a recognized medical problem in developed countries [1]. However, treatment of obesity is often unsuccessful. Weight loss can be achieved, but long-term weight maintenance after weight loss is rarely shown [2–4]. Therefore, identification of substances that increase satiety or at least sustain satiety during energy restriction is needed. One possible way to improve satiety is to increase hepatic fatty acid oxidation [5]. Therefore, finding ways to stimulate hepatic fatty acid oxidation should be promising for appetite and weight control. In this experiment, we propose to interfere in postingestive modulation of fat-induced satiety by stimulating hepatic fatty acid oxidation. We therefore investigated the potential of (−)-hydroxycitrate (HCA), which is believed to induce hepatic fatty acid oxidation [6–8], and medium-chain triglycerides (MCT), which are more readily oxidized [9–12], to increase satiety.

HCA is an active ingredient that is extracted from the rind of the fruit *Garcinia cambogia*, a native species to India, and is promoted as a weight loss agent. HCA is an inhibitor of ATP-citrate-lyase, a cytosolic (extramitochondrial) enzyme that catalyzes the cleavage of citrate to oxaloacetate and acetyl-CoA [6,13,14]. The effect of HCA would therefore be to reduce the acetyl-CoA pool, limiting the availability of 2-carbon groups required for the synthesis of fats and cholesterol. In this respect, HCA might promote weight maintenance by inhibiting or limiting the capacity for de novo lipogenesis [13]. Furthermore, HCA might induce weight loss through increased satiety by increasing fatty acid oxidation [15,16], probably by inhibition of acetyl-CoA and subsequently of malonyl-CoA formation that, in turn, would stimulate carnitine transferase activity, or by increasing the rate of glycogen synthesis in the liver [17]. Up to now, however, the results on the effects of HCA on appetite, body weight (BW), and energy

* Corresponding author. Tel.: +31-43-388-21-23; fax: +31-43-367-09-76.

E-mail address: e.kovacs@hb.unimaas.nl (E.M.R. Kovacs).

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expenditure, and its possible contribution as a weight loss agent in humans, are controversial [18–21]. Several studies found a positive effect of HCA administration alone or in combination with other ingredients on appetite, energy intake, BW loss, or energy expenditure [22–27], but others did not [28–32].

MCT have been repeatedly suggested to contribute to the control of BW. MCT are known to be rapidly hydrolyzed and absorbed [33,34]. It has been shown that fatty acids delivered by MCT are preferentially oxidized and poorly stored within tissues, and that MCT have a marked thermic effect [35]. In addition to that, MCT have been shown to have satiating properties and to decrease food intake [11,12,36] by involving a cascade of preabsorptive and postabsorptive mechanisms. However, the exact mechanism underlying the reduction in food intake after MCT ingestion is not fully understood [33,37].

In a previous study, we concentrated on the effects of HCA and HCA combined with MCT on energy expenditure while feeding subjects in energy balance [32]. In the present study, we concentrated on the effects of HCA and HCA combined with MCT on satiety and energy intake during ad libitum feeding.

Therefore, the aim of the present study was to investigate the effects of chronic ingestion of HCA and MCT on satiety and energy intake. We hypothesized that HCA supplementation might affect BW regulation by inducing satiety and reducing food intake. We further hypothesized that the combination of HCA and MCT may have a stronger effect on satiety compared to HCA alone.

2. Methods

2.1. Subjects

Seven male and 14 female normal to moderately obese subjects participated in this study. The subjects were recruited by advertisements in local newspapers, in which we asked for moderately obese male and female subjects who wanted to participate in a study on the effects of natural food supplements on appetite, food intake, and BW. Selection took place following health criteria (no diabetes, no cardiovascular diseases, no medical treatment) and BW criteria (body mass index: 24–32 kg/m^2). Baseline characteristics are presented in Table 1. The nature and risks of the experimental procedure were explained to the subjects, and all subjects gave their written informed consent. The study was approved by the Ethics Committee of Maastricht University.

2.2. Experimental design

The experiment had a double-blind, placebo-controlled, randomized, crossover design. The experimental design consisted of three intervention periods of 2 weeks separated by washout periods of 2 or 6 weeks (Fig. 1) to ensure that the women were always in the same phase of the menstrual cycle. Statistical analysis (*t*-test) of the results revealed that there were no differences between the washout periods of 2 or 6 weeks, with respect to the energy intake on the test day.

Table 1
Subjects characteristics at baseline

	Mean ± S.D.	Range
Age (years)	43 ± 10	29–57
Height (m)	170 ± 8	155–180
Weight (kg)	79.3 ± 9.0	61.2–93.0
Body mass index (kg/m^2)	27.6 ± 2.0	24.0–31.5
Waist circumference (cm)	88 ± 8	74–104
Hip circumference (cm)	104 ± 6	95–116
WHR	0.85 ± 0.08	0.74–1.01
F1 (cognitive restraint)	8 ± 3	1–14
F2 (disinhibition)	6 ± 3	1–11
F3 (hunger)	5 ± 3	0–10
Herman and Polivy restraint	16 ± 5	6–30

n = 21 subjects (7 men and 14 women).
F1–F3: Factors 1–3 of the TFEQ.

During the washout periods, the subjects consumed a self-selected and self-prepared diet. During the intervention periods, the subjects consumed at home three self-selected and self-prepared meals daily (breakfast, lunch, and dinner) with no restriction regarding type and amount of food. They were instructed to drink maximally one glass of alcoholic beverage per day. Between the meals, the subjects consumed an isoenergetic snack (cereal bar) of 22 g (energy, 420 kJ; protein, 0.7 g; fat, 4 g; carbohydrate, 14 g; dietary fibre, 0.5 g) with no supplementation (PLA), with supplementation of 500 mg HCA (850 mg SuperCitrimax HCA 600 SXG, HCA content: 58.81%, EuroChem Feinchemie, München, Germany), or 500 mg HCA and 3 g MCT (HCA + MCT). The dosage of HCA used was similar or even higher to that used in several studies in which an effect of HCA on BW loss was found (500 mg, 3 times/day [22,23]; 55–110 mg, 2 times/day [24]). The snacks were consumed at four fixed time points: 1 h before lunch, 2 h after lunch, 1 h before dinner, and 2 h after dinner. The snack was used for practical comfort, because HCA (powder) and MCT (oil) could be easily incorporated into the product. Between the meals, the subjects were not allowed to eat with exception of the prescribed snacks. They were allowed to drink ad libitum water, coffee, and tea (without sugar and milk).

2.3. Anthropometry

BW was measured during screening, at the beginning, after 1 week and at the end of each intervention period on a digital balance accurate to 0.02 kg (Chyo-MW-150K, Japan) with subjects in underwear, in the fasted state, and after voiding their bladder. Height was measured to the nearest 0.1 cm during screening using a wall-mounted stadiometer

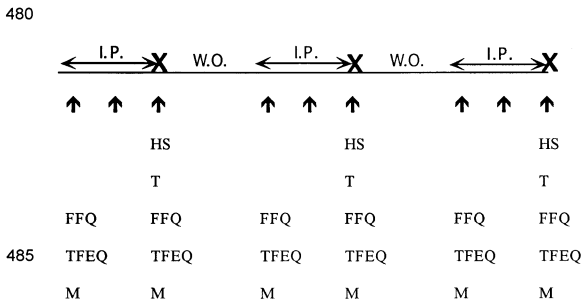

Fig. 1. Experimental design. I.P. = intervention periods; W.O. = washout periods; × = test day; ↑ = measurement of body weight; HS = questionnaires on hunger and satiety; T = questionnaire on tolerance; FFQ = food frequency questionnaire; TFEQ = questionnaires on eating behavior; M = questionnaire on mood.

(Seca, model 220, Hamburg, Germany). The body mass index was calculated by BW/height^2 (kg/m^2).

The distribution of fat was investigated during screening by measuring the waist and hip circumferences and calculation of the waist–hip ratio (WHR). The waist circumference was measured at the site of the smallest circumference between the rib cage and the ileac crest, with the subjects in standing position. The hip circumference was measured at the site of the largest circumference between the waist and the thighs. The WHR was calculated by dividing the waist circumference by the hip circumference.

2.4. Eating behavior

Eating behavior was analyzed during screening, at the beginning, and at the end of each intervention period using a validated Dutch translation of the Three-Factor Eating Behavior Questionnaire (TFEQ) [38,39]. Cognitive restrained and unrestrained eating behavior (Factor 1), emotional eating and disinhibition (Factor 2), and the subjective feeling of hunger (Factor 3) were scored. BW concern and chronic dieting behavior were investigated with the Herman and Polivy questionnaire (HP) [40] during screening, at the beginning, and at the end of each intervention period.

2.5. Daily energy intake

Energy intake over the previous week was recorded at the beginning and at the end of each intervention period using a food frequency questionnaire. Personal instruction was given in advance. The questionnaires were analyzed using the Dutch food composition table [41] and the accessory computer program (Becel Nutrition Program 1988). Daily energy intake before and during intervention was compared with predicted 24-h energy expenditure [42] that amounted, on the average, to 10.6 ± 0.3 MJ/day in all treatments. Since this was significantly higher compared to the reported energy intakes (before intervention: PLA, 7.4 ± 0.5 MJ/day; HCA, 6.9 ± 0.5 MJ/day; HCA + MCT, 7.3 ± 0.6 MJ/day; during the second week of intervention: PLA, 8.0 ± 0.5 MJ/day; HCA, 7.7 ± 0.4 MJ/day; HCA + MCT, 7.8 ± 0.4 MJ/day), these data were not further used to express daily energy intake.

2.6. Mood

Mood questionnaires were completed at the beginning and at the end of each intervention period [43]. The subjects indicated on anchored 100-mm visual analogue scales ranging from "not at all" to "extremely" how relaxed, gloomy, fine, angry, scared, and sad they felt.

2.7. Tolerance

Tolerance questionnaires were completed at the end of each intervention period. The subjects indicated on a five-point scale questionnaire (0 = *not at all*, 1 = *less*, 2 = *sometimes*, 3 = *relatively much*, 4 = *very much*) how intensively they experienced unwell feeling, headache, weakness, tiredness, nausea, vomit, eructation, abdominal pain, bloating, flatulence, constipation, diarrhea, dryness in the mouth, changes in taste, increased sweat production, and increased thirst.

2.8. Test day

At the end of each intervention period, the subjects were invited for an experiment in the laboratory assessing 24-h energy intake and appetite profile.

The subjects arrived between 07:30 and 09:00 h, always at the same day of the week and at the same time of the day. They received a standardized breakfast, consisting of bread, butter, cheese, coffee, or tea. After breakfast, they left and returned between 12:00 and 13:00 h for lunch. Lunch, consisting of bread (brown, white), a choice of sweet and savory bread filling (jam, chocolate vermicelli, cheese, and ham), and different kinds of drinks (milk, tea, and coffee), was consumed ad libitum. The subjects returned again between 17:00 and 18:30 h for dinner. Dinner, which consisted of a cooked meal (pasta or nasi for vegetarians) and a dessert, was also consumed ad libitum. The foods offered during the test day were typical Dutch items, according to food consumption surveys [44]. Between the meals, the subjects were not allowed to eat with exception of the prescribed snacks, water, coffee, and tea (without sugar and milk). Energy intake and food selection were determined.

Appetite profile during the day was scored on anchored 100-mm visual analogue scales and completed at 10 fixed time points, respectively, immediately before and after breakfast, in the morning between 10:00 and 11:00 h, immediately before and after lunch, in the afternoon between 14:30 and 15:30 h, immediately before and after dinner, in the evening between 21:00 and 22:00 h, and before sleeping [39].

2.9. Statistical analysis

Data are presented as means ± standard error (S.E.). Differences between the treatments were determined by analysis of variance (ANOVA) for repeated measures and Sheffe's F post hoc test (Statview SE Graphics). The measurements at the beginning and at the end of the experiment were compared using paired t-tests. Pearson correlation coefficients, r, were calculated to determine the relationship between selected variables. The level of significance was set at $P < .05$.

3. Results

There was a significant BW loss during the 2 weeks of treatment for the whole group (PLA, -0.5 ± 0.3 kg, $P < .05$; HCA, -0.4 ± 0.2 kg, $P < .05$; HCA + MCT, -0.7 ± 0.2 kg; $P < .01$). However, BW reduction was not different between treatments for the whole group, as well as for the men and women apart. BW loss was greater during the first compared to the second and third intervention periods (-1.2 ± 0.5 kg vs. -0.2 ± 0.2 and -0.3 ± 0.2 kg, respectively; $P < .001$).

Scores on the HP and the TFEQ questionnaires were similar for all treatments and did not change during treatment.

There was no difference in mood before and after intervention between treatments. The snacks were well tolerated and values for complaints remained low. The snacks were similarly tolerated in all treatments.

Twenty-four-hour energy intake during the test day for the whole group was similar in all treatments (PLA, 8.1 ± 0.3 MJ; HCA, 8.4 ± 0.2 MJ; HCA + MCT, 8.4 ± 0.3 MJ). Twenty-four-hour energy intake was similar in all treatments for both men (PLA, 9.4 ± 0.3 MJ; HCA, 9.2 ± 0.2 MJ; HCA + MCT, 9.3 ± 0.3 MJ) and women (PLA, 7.4 ± 0.2 MJ; HCA, 7.9 ± 0.2 MJ; HCA + MCT, 7.9 ± 0.3 MJ). Twenty-four-hour energy intake was lower compared to predicted 24-h energy expenditure (10.6 ± 0.3 MJ [42]) in all treatments, confirming that the subjects were in a negative energy balance during the test day. Energy intake was similar for all treatments during breakfast and dinner, but was higher with HCA compared to PLA during lunch (PLA, 2.2 ± 0.2 MJ; HCA, 2.6 ± 0.1 MJ; $P < .05$; Fig. 2). Energy intake during lunch was different between HCA and PLA in women (PLA, 2.0 ± 0.1 MJ; HCA, 2.5 ± 0.2 MJ; $P < .01$), but not in men. No relationship was found between Factor 1 of the TFEQ (cognitive restrained/unrestrained eating behavior) and the difference in energy intake during lunch between the HCA and the PLA treatments ($r = .05$).

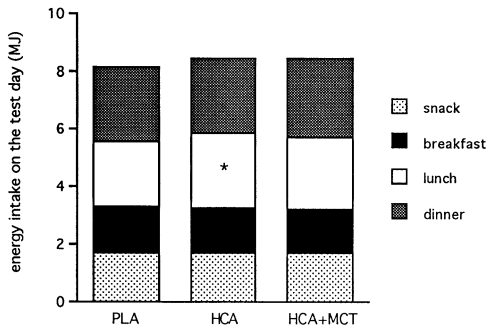

Fig. 2. Energy intake during the test day. Values are means. PLA = placebo; HCA = (−)-hydroxycitrate; MCT = medium-chain triglycerides. Statistical significance was determined by an analysis of variance (ANOVA) for repeated measures. * HCA significantly different from PLA ($P < .05$) during lunch.

Table 2
Area under the curve from the following 100-mm visual analogue scale ratings completed at 10 fixed time points over 16 h (mm.h)

	PLA	HCA	HCA + MCT	P
Hunger	436 ± 37	463 ± 30	462 ± 33	ns
Appetite	540 ± 39	504 ± 35	527 ± 32	ns
Anticipated food intake	540 ± 39	534 ± 42	558 ± 54	ns
Desire to eat	494 ± 35	497 ± 31	471 ± 30	ns
Fullness	636 ± 42	705 ± 37	668 ± 26	ns
Satiety	691 ± 30	733 ± 32	714 ± 25	ns
Thirst	575 ± 30	643 ± 38	616 ± 40	ns

Values are means ± S.E. PLA = placebo; HCA = (−)-hydroxycitrate; MCT = medium-chain triglycerides. Statistical significance was determined by an analysis of variance (ANOVA) for repeated measures. ns = no significance.

The ratings on the appetite-related questions throughout the day, expressed as area under the curve (AUC) over 16 h, corrected for the subject's minimum score, are shown in Table 2. The AUC of these parameters were not different between the three treatments. Hunger scores at 20:30 h and thirst scores after lunch were higher with HCA compared to PLA ($P < .05$ and $P < .01$, respectively).

Compliance to the snacks was determined by asking the subjects how many snacks were left. A mean of 98% of the snacks was consumed, indicating a very high compliance to the snacks.

4. Discussion

In the present study, we investigated the potential of HCA and MCT on satiety, energy intake, and BW control. The results did not support the hypothesis that HCA induces satiety and reduces energy intake, in these subjects, losing BW.

Results on the effectiveness of HCA ingestion in human studies are controversial. Our findings are in contrast with several studies that observed decreased appetite [22,25], reduced 24-h energy intake [26] or increased BW and/or fat loss [22–25] after ingestion of HCA alone or in combination with other ingredients. However, other studies also failed to find significant effects of HCA on BW loss [28,29] or energy expenditure [30–32].

One possible reason why HCA did not reduce appetite and food intake in the present study is the state of

negative energy balance of the subjects as shown by the mean BW loss of 0.5 kg during the 2 weeks of intervention. BW loss probably resulted from a diet regimen that prescribed to refrain from food ingestion in between the meals with exception of the given snacks and noncaloric beverages and to minimize alcohol consumption. Because of this weight loss in all subjects, the possible effect of HCA, i.e., increase of satiety, reduction of food intake and inhibition of fat synthesis, would have had to occur in a negative energy balance. This is unlikely, since the conversion of citrate into acetyl-CoA by ATP-citrate-lyase only occurs when energy intake exceeds the energy requirements of the body. When the energy requirements of the body are not met, carbohydrate will be used in the citric acid cycle to produce ATP for energy rather than to form citrate, the substrate for de novo fatty acid synthesis. It is therefore likely that the ATP-citrate-lyase is relatively inactive when the subjects are in a negative energy balance. Consequently, HCA would be ineffective in inhibiting fat synthesis [20]. The ineffectiveness of HCA when the subjects are in a negative energy balance has also been observed in other studies [28,29]. In addition, Westerterp-Plantenga and Kovacs [26] found a reduced 24-h energy intake in weight stable subjects as a result of HCA ingestion using a similar experimental design, and Mattes and Bormann [27] found a greater food intake reduction and BW loss using HCA during 12 weeks compared to placebo.

Negative energy balance was much greater during the first intervention (-1.2 kg) compared to the second and third intervention (-0.2 and -0.3 kg, respectively). Therefore, HCA and HCA combined with MCT would have had a greater opportunity to show effectiveness during these two latter interventions. We also examined the results after having removed the data from the first intervention. We did not find any effect of HCA on energy intake or appetite-related parameters during the test day. However, when the subjects started with the second and third intervention, they were already in a situation of negative energy balance compared to baseline (-0.7 and -0.2 kg, respectively), as they did not completely regain the weight lost during the first intervention.

Although 24-h energy intake was similar for all treatments, energy intake during lunch was higher with HCA compared to PLA, in the women, this in contradiction to the original hypothesis. We do not have a direct explanation for this, as energy intake for breakfast and with snacks was standardized and no difference in energy intake during dinner was found between treatments. Dietary restraint is unlikely to have played a role in the higher energy intake during lunch with HCA compared to PLA.

The negative result on the effectiveness of HCA could potentially be affected by its bioavailability. Water solubility and pH level are two major components of bioavailability that may differ between HCA compounds available on the market. A compound complexed with calcium and potassium, like the one used in the present study, is nearly 100% soluble and creates a pH level that is favorable for maximal gastrointestinal absorption [19]. In our laboratory, bioavailability of HCA supplemented in humans has been assessed by van Loon et al. [31]. It was shown that ingestion of a single dose of HCA (4.4 g) resulted in maximal plasma HCA concentration after 60–90 min (0.12 mmol/l $\approx$ 1.4% of the administered HCA, assuming 4.5 l blood and a hematocrit of 45%) and that HCA remained present at least for 3 h. Therefore, we assume that in our study with sustained administration of HCA, low concentrations of HCA were continuously present in plasma.

Whereas MCT have been repeatedly shown to have satiating properties and to reduce food intake in humans [11,12,36], we found no additional effect of MCT on satiety, food intake, or BW loss. However, these studies used a different study protocol and/or a higher dosage MCT. Stubbs and Harbron [12] observed that substitution of LCT with MCT (65% fat) in high-fat, high-energy diets for 14 days decreased energy intake. Van Wymelbeke et al. [36] found that a breakfast supplemented with MCT (43 g) decreased energy intake during a free-choice lunch. Rolls et al. [11] found that a small preload of MCT (ca. 18, 36, or 54 g) incorporated into a liquid meal was more effective at suppressing energy intake of a subsequent meal presented 30 min later, compared to LCT, already with the lowest dosage. In the present study, a lower dosage of MCT (12 g/day) was used. The maximal amount of oral MCT that can be tolerated in the gastrointestinal tract is small. Ivy et al. [45] reported that administration of 30 g MCT, in combination with cereal, caused some minor distress in 10% of the subjects. This was a reason why we kept the MCT dosage low, as supplementation lasted for 2 weeks. Although the supplementation occurred for a 2-week period, this low dosage might explain why no effect of MCT was found on energy intake. Furthermore, in the present study, MCT was not investigated alone. Therefore, we cannot make statements about the efficacy of MCT themselves. Since HCA was not effective in the present study, it is possible that a possible additional effect of MCT was inhibited.

The supposed effectiveness of HCA through inhibition of de novo lipogenesis, increased hepatic fatty acid oxidation, and promotion of glycogen stores preservation did not appear under these circumstances. Under negative energy balance conditions, de novo lipogenesis and preservation of glycogen reserves are highly unlikely to appear. The only possible remaining mechanism is an increased hepatic fatty acid oxidation. Since we did not measure hepatic fatty acid oxidation in the present study, we cannot draw a firm conclusion on that aspect. It might be argued that a 2-week intervention is too short to demonstrate significant effects of HCA or HCA combined with MCT on appetite or BW. However, Westerterp-Plantenga and Kovacs [26] did observe a reduced 24-h energy intake with HCA using a similar 2-week intervention protocol in weight stable sub-

jects, although this effect was not reflected in BW changes. In addition, Goris and Westerterp [46] showed that 2 weeks are sufficient for BW effects.

In summary, we showed that HCA and HCA combined with MCT were not effective with respect to satiety and energy intake under a negative energy balance condition.

Acknowledgments

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