Review

(-)-Hydroxycitrate Ingestion and Endurance Exercise Performance

Kiwon Lim1*, Sungpil Ryu2, Heajung Suh3, Kengo Ishihara4 and Tohru Fushiki5

1Department of Physical Education, Konkuk University, Seoul 143–701, Korea
2Department of Leisure Science and Recreation, Sangji National University, Sangju, 741–711, Korea
3Department of Physical Education, Sejong University, Seoul 143–747, Korea
4Department of Food and Nutrition, Saga University, Saga 849-8502, Japan
5Laboratory of Nutritional Chemistry, Division of Food Science and Biotechnology, Kyoto University, Kyoto 606–8502, Japan

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Summary  We have been interested in the ergogenic aid effects of food components and supplements for enhancing endurance exercise performance. For this purpose, acute or chronic (-)-hydroxycitrate (HCA) ingestion might be effective because it promotes utilization of fatty acid as an energy source. HCA is a competitive inhibitor of the enzyme ATP:citrate lyase, thereby increasing inhibition of lipogenesis in the body. Many researchers have reported that less body fat accumulation and sustained satiety cause less food intake. After focusing on exercise performance with HCA ingestion, we came up with different results that show positive effects or not. However, our previously reported data showed increased use of fatty acids during moderate intensity exercise. For future research, HCA and co-ingestion of other supplements, such as carnitine or caffeine, might have greater effect on glycogen-sparing than HCA alone.

Key Words  (-)-hydroxycitrate (HCA), RER, fat oxidation, endurance exercise performance

Many dietary supplements have been investigated in the sports field to improve performance in endurance exercise. There have been numerous reports over the past decades demonstrating the importance of muscle and liver glycogen content in reducing fatigue and improving athletic performance. In fact, several studies revealed that the most important factor might be the glycogen-sparing effect during exercise accompanied by an increase in the ability of skeletal muscle to oxidized lipids (1). This is because when muscle glycogen and blood glucose concentrations are low, the intensity of exercise must be reduced to a level that can be supported by the limited ability of the body to convert fat into energy (2).

The glycogen-sparing effect has been emphasized because high carbohydrate ingestion before competition increases the total body water content and the body weight. Therefore, nutritional ergogenic aids are suggested for lipids as an alternative energy source during endurance exercise performance. Focusing on these suggestions, many researchers (3) have proposed caffeine ingestion for increasing lipolysis through elevation in blood catecholamine concentrations, which enhance fat oxidation by increasing circulating levels of free fatty acids (FFA) (5). We have indicated caffeine (5), capsaicin (6), and red pepper (7) as lipolytic food components and carnitine (9) as a factor involved in long chain fatty acid oxidation. These components were shown to affect the endurance performance in animals and humans.

Endogenous epinephrine secretion is increased by exercise and hypoxia (10) as well as by caffeine ingestion (3). It is well known that an increase in endogenous epinephrine secretion results in a concomitant increase in intramuscular glycogen utilization because glycogen phosphorylase activity is elevated by β-adrenergic stimulation (11). Therefore, caffeine ingestion 1 h prior to exercise induces lipolysis (5) and glycogenolysis (12) simultaneously, resulting in increased blood FFA and lactate accumulation. This would cause fatigue. In other words, caffeine ingestion does not positively affect endurance exercise performance in untrained humans (5), although it induced higher FFA concentrations and improved endurance performance in trained subjects (3). Douglas et al. (13) reported that caffeine ingestion increases the blood lactate concentration at the earlier stages of exercise without enhancing exercise performance time. Therefore, less lactate accumulation during exercise is important for glycogen sparing.

Evidence suggests that (-)-hydroxycitrate (HCA) does not stimulate lactate release from skeletal muscle during exercise. In the present review, therefore, attempts have been made to pool and summarize the available information on the physiological aspects of HCA.

*To whom correspondence should be addressed.
E-mail: kwlim21@hotmail.com
Functions of HCA

HCA is a principal constituent of the rind of Garcinia cambogia, a spice that is used in curries and condiments in India and South-East Asia. The pilot study of Van Loon et al. (14) has shown that ingested HCA is absorbed in the gastrointestinal tract and enters the systemic circulation; this event is of primary importance for the HCA-induced effect on skeletal muscle fuel selection.

HCA, a potent inhibitor of ATP: citrate lyase (EC 4.1.3.8) (15), inhibits fatty acid synthesis and reduces appetite in rodents (15) and also increases the rates of hepatic glycogen synthesis and induces a decrease in body weight gain (17). The ATP: citrate lyase, a cytosolic enzyme, cleaves citrate so that the resulting acetyl-CoA can be used in fatty acid synthesis and other biosynthetic processes (18).

HCA ingestion might also have an effect on fat oxidation because extramitochondrial cleavage of citrate is the penultimate step in the conversion of glucose into malonyl-CoA, suggesting that ingestion of HCA could reduce cytosolic malonyl-CoA concentrations and increase fatty acid oxidation (19). The addition of HCA resulted in an approximately 50% decrease of acetyl-CoA content in platelet cytoplasm of control and diabetes patients with no significant changes of its levels in mitochondria (20).

Malonyl-CoA is an inhibitor of carnitine palmitoyltransferase I (CPT I), the enzyme that controls the oxidation of fatty acids by regulating their transport into mitochondria. In other words, reduced cytosolic malonyl-CoA concentrations can promote fat oxidation by a diminished inhibitory effect on CPT I activity (21).

As shown in Fig. 1, fatty acid synthesis is conversely related to fatty acid oxidation. In this paradigm, malonyl-CoA concentration increases during fatty acid synthesis and results in inhibition of CPT I which mediates uptake of fatty acids into mitochondria in the muscle cells. Precisely when the TCA cycle is highly active, and citrate is thus generated rapidly, a portion of this citrate migrates to the cytoplasm where it can be cleaved by ATP: citrate lyase to yield cytoplasmic acetyl-CoA. Cytoplasmic acetyl-CoA then can be converted into malonyl-CoA in a reaction catalyzed by acetyl-CoA carboxylase. Resulting malonyl-CoA in turn not only serves as a substrate for lipogenesis, but also inhibits CPT I allosterically, suppressing fatty acid oxidation (22). Zambell et al. (23) found that the ATP: citrate lyase activity in colonocyte was depressed 86.6% by 7 mmol/L of HCA. Suppression of cytoplasmic acetyl-CoA production by HCA indicates that ATP: citrate lyase plays an important role in the maintenance of a stable level of acetyl-CoA in the cytoplasmic compartment (20).

HCA and Lipogenesis

HCA administration was shown to significantly inhibit the rates of lipogenesis in rodent liver, adipose tissue and small intestine (15). When HCA was added to incubated adipose tissue, synthesis of fatty acids from [2-14C] pyruvate was inhibited to similar extents in rats and rabbits (26). The action of HCA should reduce the acetyl-CoA pool, thus limiting the availability of 2-carbon units required for fatty acid and cholesterol biosynthesis (14). Sudgen et al. (25) reported that increased lipogenesis in brown adipose tissue in response to glucose feeding was inhibited by HCA administration. In starved rats, however, HCA did not inhibit the brown adipocyte lipogenesis and glucose utilization. Moreover, HCA is a positive effector for acetyl-CoA carboxylase. The similarity of HCA and citrate for the activation of the enzyme is apparent in regard to the time for maximal stimulation of the enzyme activity, 30 min or more (27).

HCA decreased insulin-stimulated fatty acid synthet-
Table 1. Effect of 3.3% of G. cambogia rind fruit extract on food intake, body weight, and blood profiles change in mice fed 10% sucrose water for 4 wk.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=7)</th>
<th>Treated (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food consumption (g/4 wk)</td>
<td>144(9)</td>
<td>132(9)</td>
</tr>
<tr>
<td>Sucrose water consumption (mL/4 wk)</td>
<td>362(33)</td>
<td>304(40)</td>
</tr>
<tr>
<td>Body weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial (g)</td>
<td>30.3(0.3)</td>
<td>30.6(0.6)</td>
</tr>
<tr>
<td>Final (g)</td>
<td>37.6(1.4)</td>
<td>37.3(1.8)</td>
</tr>
<tr>
<td>Ratio of body weight increase (%)</td>
<td>122(4)</td>
<td>124(4)</td>
</tr>
<tr>
<td>Total white adipose tissue (g)</td>
<td>2.50(0.55)</td>
<td>2.47(0.58)</td>
</tr>
<tr>
<td>Blood profiles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>161(9)</td>
<td>137.7(8.6)</td>
</tr>
<tr>
<td>Triacylglycerol (mg/dL)</td>
<td>148(15)</td>
<td>96(12)*</td>
</tr>
<tr>
<td>FFA (mEq/L)</td>
<td>3.26(0.24)</td>
<td>2.26(0.19)*</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>178(18)</td>
<td>174(18)</td>
</tr>
<tr>
<td>Insulin (ng/mL)</td>
<td>3.52(0.63)</td>
<td>1.83(0.20)*</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>11.7(3.3)</td>
<td>5.8(1.3)</td>
</tr>
</tbody>
</table>

Values are mean and (S.E.M). *Data from Ref. 30. *p<0.05.

sis from [6-14C] glucose to 10% of control (28). In addition, Chen et al. (29) reported that HCA inhibited the glucose-stimulated insulin secretion from β-cells and provided evidence for the pivotal role of malonyl-CoA in the suppression of CPT I in association with elevated cytosolic long chain acyl-CoA concentration in the normal pancreatic β-cell. Insulin resistance has been associated with glucose intolerance and dyslipidemia and has been observed in patients with visceral fat accumulation. Compared with subcutaneous adipose tissue, intra-abdominal fat pads take up more glucose under insulin stimulation (30).

A 12-wk evaluation period failed to support the hypothesis that HCA would promote a decrease in fat mass beyond that observed with a placebo (31); however, this report has a crucial limitation: HCA was administered with a high-fiber and low-energy diet. A high-fiber diet might interfere with the absorption of HCA in the gastrointestinal tract and a low-calorie diet might not result in increased energy metabolism.

Hood et al. (32) have shown that HCA reduces the synthesis of fatty acids from lactate and glucose in bovine adipose tissue and rat adipose tissue, respectively, and suggested that the conversion of lactate to fatty acids probably occurs by a pathway involving citrate. Chee et al. (33) reported that the rate of hepatic fatty acid synthesis is depressed by a single intraperitoneal injection of HCA in rats and chickens.

HCA equivalently reduced the biosynthesis of triglycerides, phospholipids, cholesterol, diglycerides, and free fatty acids in isolated liver cells from normal and hyperlipidemic rats (34). Another possible mechanism is that HCA might increase satiety, thus resulting in reduction of food intake and consequent inhibition of fat synthesis. Therefore, this would lead to a negative energy balance (35, 36). In addition, Mattes and Bormann (37) reported that greater food intake reduction and body weight loss occur in HCA ingestion during 12 wk than in a placebo control. A possible mechanism is that the effect of HCA might be related to an increase in hepatic fatty acid oxidation due to suppressed formation of the CPT I inhibitor malonyl-CoA (38). Similarly, after restriction feeding periods, HCA ingestion reduced body weight regain in rats for at least 22 d of ad libitum feeding with diets containing 1 and 12% fat (36). Even when mice were provided with water containing 10% of sucrose for 4 wk energy gain from food and sucrose tended to be reduced by HCA ingestion, without body weight gain (Table 1) (30).

As shown in Table 1, the adipose tissue-decreasing effect of Garcinia cambogia fruit rind extract was not detected for 3.3% of HCA-added diet, instead of cellulose, for 4 wk. In addition, Ishihara et al. (39) have reported that administration of 10 mg HCA twice a day for 25 d did not affect food intake or body fat accumulation in trained mice (Fig. 2). However, Hayamizu et al. (30) have reported that blood lipids and the insulin/glucose ratio were lowered by G. cambogia extract ingestion and serum leptin concentration was slightly decreased, without significance.
The mechanism underlying the effect of HCA on energy expenditure remains unclear. HCA may increase energy expenditure in part by increasing glycogen storage through indirect pathways. For example, it might be through extrahepatic glycolysis followed by hepatic gluconeogenesis, which is thermogenic (40). Increased blood ketones and hepatic glycogen levels have been proposed as potential mechanisms for the satiety effect of HCA (41). Kim et al. (42) reported that HCA ingestion increased glycogen storage significantly during carbohydrate-loading periods with less fat accumulation and enhanced endurance exercise capacity.

**HCA and exercise performance**

The inhibition of ATP: citrate lyase by HCA causes less dietary carbohydrate to be utilized for the synthesis of fatty acids, resulting in augmented glycogen storage in the liver and muscles (43). HCA supplementation has been suggested as an ergogenic aid, especially because an increase in fatty acid oxidative capacity would limit endogenous carbohydrate utilization during aerobic exercise (19). There is also the hypothesis that the conversion of citrate to acetyl-CoA by ATP: citrate lyase occurs only when the rate of glycolysis exceeds the energy requirement of the body. Cytosolic malonyl-CoA reduces uptake of FFA into the mitochondria where FFA are oxidized. In addition, acetyl-CoA concentrations increase during fat oxidation and bring about increased malonyl-CoA in the cytosol, which in turn suppresses CPT I activities. Therefore, reduced fat oxidation results in increasing carbohydrate oxidation. Endurance exercise performance might be enhanced in association with the increased fat oxidation brought about by HCA ingestion.

When compared to administration of 10 mg or 30 mg of HCA in mice, acute ingestion of a lower amount of HCA could reduce the respiratory exchange ratio (RER). It was reported that serum FFA levels were increased significantly 100 min after a single oral administration of 10 mg HCA (39). The responsible mechanism, however, was different from fat mobilization.
tion by caffeine and capsaicin. Our previously reported data indicated that plasma glycerol concentration was not significantly different between 125 mg of HCA in tablet and placebo tablet trials (44). This suggests that fat mobilization by chronic HCA ingestion does not occur during endurance exercise performance. Moreover, FFA concentration was significantly higher in HCA than in the placebo at 80% VO2max exercise, suggesting that during moderate intensity exercise in trained athletes (44) and exercise at 60% VO2max in untrained men (45) chronic ingestion of HCA elicits preferential use of fatty acids as an energy source. Thus, enhancement of lipid oxidation at the early stages of exercise could lead to increase endurance capacity.

As shown in Fig. 3, Ishihara et al. (39) reported that HCA ingestion for 13 d increased fat oxidation and improved endurance exercise time to fatigue by 43% compared to a placebo in mice. They proposed that chronic administration of HCA promotes fat oxidation and spares carbohydrate utilization in mice at rest and during exercise.

Kriketos et al. (46) have reported that acute ingestion of HCA does not support the hypothesis that HCA might alter the short-term rate of fat oxidation in the fasting state during rest or moderate exercise. Their results showed that RER and energy expenditure were not changed between HCA and placebo ingestion in non-trained, 3-d-fasting adult males during rest and during cycle ergometer exercise. In addition, although ingestion of a large amount (19 g) of HCA increased plasma HCA concentration, it did not affect fatty acid oxidation or RER during exercise in trained cyclists (14). It was suggested that the absence of effect on fat oxidation could be explained by the already increased oxidative capacity in the endurance-trained cyclists, although less lactate accumulation was found in subjects administered with HCA during exercise time.

The negative results on the effectiveness of HCA could potentially be affected by its bioavailability. Water solubility and pH level of the HCA preparations are two major components of bioavailability, and may differ among preparations available on the market (35). However, the HCA used in their study was not a water-soluble, calcium-attached formula. Calcium-salt powder is stable but not ideal for food products due to its insolubility in water. For HCA extraction, calcium, potassium, and sodium were used (43). Among them, the calcium-salt was less absorbed in the intestine compared to the sodium-salt. Excessive levels of calcium (used to stabilize the HCA molecule) and low solubility in water are known to exist in many, but not all, commercial HCA preparations (47). We (44, 48) have reported that short-term ingestion of sodium-salt HCA significantly increases fat oxidation and decreases carbohydrate oxidation during moderate and high intensity cycle ergometer exercise in athletes (Fig. 4) and tends to lower RER in untrained women (Fig. 5).

In addition, ingestion periods of HCA might lead our results to be different from those of other reports (14, 39). It might be predicted that long-term ingestion would be needed for detection of the effects of HCA on fat oxidation and the form of HCA ingested or exercise could be an important factor for these types of experiments.

During prolonged endurance exercise performance, the hepatic carnitine levels are too low to activate CPT I, which is activated by exogenous carnitine and inhibited by malonyl-CoA. Carnitine is biosynthesized from lysine and methionine in kidney and liver. However, the amount might be too small to supply the energy needed.

Table 2. Effect of (-)-HCA and carnitine ingestion on glycogen concentrations in trained rats

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>HCA</th>
<th>Carnitine</th>
<th>Co-ingestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>73.40(3.18)a</td>
<td>75.85(1.46)b</td>
<td>81.93(2.43)d</td>
<td>94.94(1.35)d</td>
</tr>
<tr>
<td>Soleus muscle</td>
<td>4.95(0.15)a</td>
<td>5.15(0.22)b</td>
<td>4.73(0.19)d</td>
<td>5.63(0.23)b</td>
</tr>
<tr>
<td>Gastrocnemius muscle</td>
<td>11.60(0.25)a</td>
<td>12.34(0.31)b</td>
<td>11.24(0.11)d</td>
<td>13.69(0.21)b</td>
</tr>
<tr>
<td>Quadriceps muscle</td>
<td>6.21(0.19)a</td>
<td>7.62(0.10)b</td>
<td>7.16(0.16)c</td>
<td>7.73(0.16)b</td>
</tr>
</tbody>
</table>

Values are mean and (S.E.M). a,b,c,d Data from Ref. 51. Statistically significant if superscripts letters are different in the horizontal column with one-way ANOVA at p<0.05.
during prolonged submaximal endurance exercise performance (49).

Sustained aerobic exercise requires a several-fold increase in hepatic glucose output. An increasing proportion of this elevated glucose output must be provided by gluconeogenesis. Thus, administration of HCA prior to endurance exercise may aid performance by enhancing gluconeogenesis. Therefore, carnitine and HCA supplementation may be more beneficial in a nutritional regimen designed to promote endurance exercise performance. We would carefully suggest that the co-ingestion of HCA and carnitine prior to exercise is useful for optimizing fat oxidation during exercise (50). We reported that 300 mg of HCA and 250 mg of carnitine co-ingestion revealed increased exercise performance and spared liver and muscle glycogen concentrations in trained rats (Table 2) (51).

In summary, we showed here that HCA intake might act as an ergogenic aid and improve endurance exercise performance. It is generally believed that sparing glycogen in endurance exercise is important to improve exercise performance. For this purpose, acute or chronic HCA ingestion might be effective in the promotion of fatty acid utilization as an energy source. Needless to say, further studies are required to clarify the effect of HCA on energy metabolism and it will be interesting to examine the effects of the combination of HCA with other supplements that enhance fat oxidation (such as carnitine and caffeine) on energy metabolism and endurance performance.

REFERENCES

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