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(+)-Catechin is a Potent Inhibitor of Intestinal Absorption of Cholesterol in Rats

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Abstract

Catechins exhibit a hypocholesterolemic effect in cholesterol-fed animals. The present study was conducted to examine whether (+)-catechin influences the absorption of cholesterol in rats. Male Sprague-Dawley rats were fed *ad libitum* an AIN-93G diet containing soybean oil for 5 wk. Rats with lymph cannulae were infused at 3.0 mL/h for 8 h via a duodenal catheter with a lipid emulsion containing radiolabeled cholesterol with or without (+)-catechin. Lymph was collected hourly for 8 h. The enteral infusion of (+)-catechin significantly lowered the lymphatic absorption of ^{14}C-cholesterol (21.1±3.6% dose/8 h) compared with controls infused with the lipid emulsion devoid of (+)-catechin (38.2±1.2% dose/8 h). The intestinal absorption of α-tocopherol (24.2±3.0% dose/8 h) also was significantly decreased by (+)-catechin infusion, relative to controls (32.2±2.2% dose/8 h). However, the lymphatic outputs of oleic acid and phospholipid were not affected by enteral (+)-catechin infusion. The results indicate that (+)-catechin has a profound inhibitory effect on the intestinal absorption of cholesterol and α-tocopherol without affecting the absorption of fat.

Key words: (+)-catechin, cholesterol, fat, intestinal absorption, α-tocopherol

INTRODUCTION

Elevated plasma cholesterol is a primary risk factor for coronary heart disease (1). Epidemiological studies (2-5) suggest that high dietary intake of flavonoids, as found in a wide variety of fruits, vegetables, seeds, and teas, may reduce the risk of coronary heart disease. Studies also have shown that blood cholesterol is decreased with increasing flavonoid consumption in animals and humans (6-8). The potential beneficial effect of dietary flavonoids has been attributed in part to their antioxidative properties, as they protect plasma low-density lipoprotein (LDL) against peroxidation due to their ability to quench free radicals. At present, however, it is still debatable whether such antioxidant properties are solely responsible for the reduced risk of cardiovascular disease.

(+)-Catechin (Fig. 1), a naturally occurring flavonoid, is widely distributed in teas, apples, grapes, red wine, pears, and chocolate (9,10). Studies have shown that (+)-catechin also exhibits an antioxidant property in preventing LDL oxidation *in vitro* and reducing aortic fatty streak accumulation in hypercholesterolemic hamsters (11,12). It is probable that fruit and vegetable-rich diets provide a significant amount of (+)-catechin that contributes to plasma antioxidant capacity.

Catechins, which belong to the flavanol subgroup of flavonoids, have been shown to exhibit hypocholesterolemic

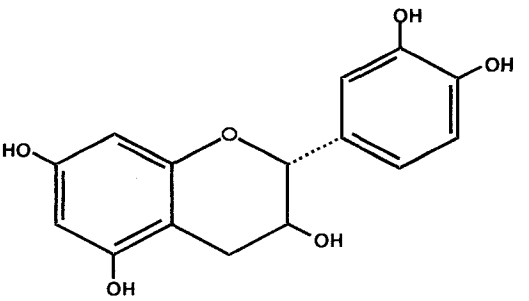

Fig. 1. The structure of (+)-catechin.

effects (13-16). Increasing evidence suggests that the cholesterol-lowering action of catechins is associated with their inhibitory effects on cholesterol absorption from the intestine. Crude tea catechin supplementation was shown to enhance fecal secretion of cholesterol in rats fed a diet containing 25% lard and 1% cholesterol for 4 wk, compared with those given the same diet free of catechins (13). Yang and Koo (14) demonstrated that tea catechins reduce blood cholesterol levels in a dose-dependent manner and increase fecal secretions of bile acids and cholesterol. The cholesterol-lowering effect appears to be independent of the hepatic activities of three major lipid-metabolizing enzymes such as 3-hydroxy-3-methyl-glutaryl-CoA reductase, cholesterol 7α-hydroxylase, and fatty acid synthase. Evidence also suggests that tea catechins may inhibit pan-

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creatic lipolytic enzymes such as lipase and phospholipase A_2 (PLA_2), thereby interfering with the luminal digestion of lipids (17-19). Most recently, we demonstrated under *in vivo* conditions that intraduodenal infusion of green tea extract or its catechins dose-dependently inhibits the intestinal absorption of cholesterol in rats (20). At present, however, whether such an inhibitory effect of tea catechins on cholesterol absorption is solely due to a specific catechin or a synergistic action of mixed catechins is yet to be elucidated. Furthermore, no information exists on whether (+)-catechin inhibits the intestinal absorption of cholesterol. The present study, as an extension of our ongoing series of studies on catechins, was conducted to determine whether (+)-catechin affects the intestinal absorption of cholesterol and other lipids in rats.

MATERIALS AND METHODS

Animals and diet

Male Sprague-Dawley rats (Harlan Sprague Dawley, Inc., Indianapolis, IN, USA) weighing 238±11 g were placed singly in plastic cages with stainless-steel wire bottoms in a animal care room maintained at 22~25°C and subjected to a daily 12-h light : dark cycle with the light period from 1530 to 0330 throughout the study. Upon arrival, rats were fed a diet (Table 1) formulated by Dyets Inc. (Bethlehem, PA, USA) according to the AIN-93G recommendations (21,22). All rats were housed in an animal care facility in the Department of Human Nutrition, Kansas State University, accredited by the American Association for the Accreditation of Laboratory Animal Care. Rats were given free access to deionized water via a stainless-steel watering system. Animals were cared for in accordance with the policies and guidelines for animal care and use procedures of the Kansas State University Institutional Animal Care and Use Committee.

Table 1. Diet composition (g/kg)

Ingredient[1)]	Amount
Egg white	200.0
Corn starch	396.5
Dextrinized corn starch	132.0
Dextrose	100.0
Cellulose	50.0
Soybean oil[2)]	70.0
Mineral mix	35.0
Vitamin mix	10.0
Biotin (1 mg/g biotin sucrose mix)	4.0
Choline bitartrate	2.5

[1)]Formulated and supplied from Dyets, Bethlehem, PA, according to the recommendations of the American Institute of Nutrition (21,22).
[2)]Contained 0.02% *tert*-butylhydroquinone.

Cannulation of the mesenteric lymph duct

At 5 wk, rats were starved for 16 h. The mesenteric lymph duct was cannulated as described previously under halothane anesthesia (23). Briefly, an abdominal incision was made along the midline. The superior mesenteric lymph duct was cannulated with polyethylene tubing (SV. 31 tubing, i.d. 0.50 mm, o.d. 0.80 mm; Dural Plastics, Auburn, Australia). An infusion catheter (Silastic medical grade tubing, i.d. 1.0 mm, o.d. 2.1 mm; Dow Corning, Midland, MI, USA) was inserted via the gastric fundus into the upper duodenum and secured by a purse-string suture (4-0 Silk; Ethicon Inc., Somerville, NJ, USA). The lymph cannula and the infusion catheter were exteriorized through the right flank and the abdominal incision was closed by suture. The rats were placed in restraining cages and housed in a recovery chamber (30°C) for postoperative recovery for 22~24 h. During this recovery period, rats were infused via the infusion catheter with phosphate-buffered saline (PBS) containing glucose (in mmol/L: 277 glucose, 6.75 Na_2HPO_4, 16.5 NaH_2PO_4, 115 NaCl, and 5 KCl; pH 6.7) at 3.0 mL/h by a syringe pump (Model 935, Harvard Apparatus, South Natick, MA, USA).

Measurement of the lymphatic absorption of ^{14}C-cholesterol

Following the postoperative recovery, each rat was infused with a lipid emulsion containing (+)-catechin at 3 mL/h for 8 h via the duodenal catheter in dim light. Lipid emulsions were prepared under a gentle stream of N_2 and subdued light using an ultrasonicator (XL-2020 Untrasonic Liquid Processor, Misonix, Farmingdale, NY, USA). The lipid emulsion consisted of 451.8 μmol triolein, 27.8 kBq ^{14}C-cholesterol, 20.7 μmol cholesterol, 3.56 μmol α-tocopherol, and 396.0 μmol sodium taurocholate with or without 689.0 μmol (200 mg) (+)-catechin (>98%, Sigma Chemical, St. Louis, MO, USA) in 24 mL of PBS. The amounts of triolein and α-tocopherol infused for 8 h were 29% and 100%, respectively, of the daily intakes of a rat consuming 20.0 g of the AIN-93G diet. The cholesterol amount infused represented a moderately high respective to other fats. During the 8-h lipid infusion, the lymph samples were collected hourly in preweighed ice-cold centrifuge tubes containing 4 mg Na_2-EDTA and 30 μg n-propyl gallate (Sigma Chemical, St. Louis, MO, USA). The hourly lymph samples (100 μL) were mixed with scintillation liquid (ScintiVerse; Fisher Scientific Co., Fair Lawn, NJ, USA) and counted to determine ^{14}C-radioactivity appearing in the lymph (Beckman LS-6500; Beckman Instruments, Fullerton, CA, USA). All samples were ice chilled and handled in subdued light.

Lipid analysis

From the lymph samples collected during the 8-h period

of lipid infusion, lipids were analyzed as follows: Phospholipid was measured colorimetrically by the method of Raheja et al. (24). α-Tocopherol was determined by a modification of an HPLC as detailed elsewhere (25,26). Total cholesterol was measured using o-phthaladehyde, as described by Rudel and Morris (27). The distributions of the lymph ^{14}C-radioactivity between free and esterified cholesterol fractions were determined by digitonin precipitation as modified previously (28,29). The digitonin precipitate (free cholesterol fraction) was counted for ^{14}C-radioactivity. An aliquot (100 µL) of hourly lymph sample also was counted to determine total ^{14}C-radioactivity. The ^{14}C-radioactivity in the esterified cholesterol fraction was calculated by total ^{14}C-radioactivity in the unfractionated lymph minus ^{14}C-radioactivity in the free cholesterol fraction.

For fatty acid analysis, total lipids from 100 µL lymph were extracted (30) by a chloroform : methanol mixture (2:1, v/v) containing 151.0 µmol/L BHT. The lipids were hydrolyzed with methanolic NaOH and fatty acids were saponified and methylated simultaneously with BF_3-methanol, as described by Slover and Lanza (31). The fatty acid methyl esters were analyzed by gas chromatography (Model 6890, Hewlett-Packard, Palo Alto, CA, USA) with an HP-INNOWax cross-linked polyethylene glycol phase capillary column (30 m, i.d. 0.25 mm; Hewlett-Packard, Wilmington, DE, USA).

Statistics

All statistical analyses were performed using PC SAS (SAS Institute, Cary, NC, USA). Repeated-measures ANOVA and the least significance difference test were used to compare group means and time-dependent changes within groups. Differences were considered significant at $p < 0.05$. Values presented are means ± SD.

RESULTS

Lymphatic absorption of ^{14}C-cholesterol

The rate of lymph flow increased significantly in response to lipid infusion in both groups. However, the rates of lymph flow did not differ between rats infused with (+)-catechin (2.2 ± 0.2 mL/h) and those with no (+)-catechin (2.5 ± 0.4 mL/h). No differences in total lymph volume were noted between groups (Table 2).

The hourly rates of ^{14}C-cholesterol absorption were significantly lower in rats infused with (+)-catechin than in controls over the 8 h period (Fig. 2, $p < 0.05$). The hourly absorption rates of ^{14}C-cholesterol for 8 h were 2.6 ± 0.4% dose/h in rats infused with (+)-catechin and 4.8 ± 0.2% dose/h in controls. Also, the cumulative absorption of ^{14}C-cholesterol for 8 h was significantly decreased in rats infused with (+)-catechin (Table 3). However, the % distribution of ^{14}C-radioactivity in the esterified cholesterol fraction did not differ between groups (Fig. 3).

The hourly rates of total cholesterol output (exogenous and endogenous) also were significantly lower in rats in-

Table 2. Cumulative lymphatic absorptions of ^{14}C-cholesterol and α-tocopherol and outputs of total cholesterol, oleic acid, total fatty acids, phospholipid, and lymph volume during 8-h duodenal infusion of a lipid emulsion containing (+)-catechin in rats

	Control	(+)-Catechin
^{14}C-Cholesterol (% dose)	38.2 ± 1.2[1)]	21.1 ± 3.6*
^{14}C-Esterified cholesterol (%)	81.8 ± 1.3	81.0 ± 1.0
Total cholesterol (µmol)	13.6 ± 1.4	10.9 ± 1.5*
α-Tocopherol (% dose)	32.2 ± 2.2	24.2 ± 3.0*
Oleic acid (µmol)	390.3 ± 43.3	420.0 ± 48.2
Total fatty acids (µmol)	534.6 ± 56.5	545.8 ± 50.1
Phospholipid (µmol)	25.3 ± 1.9	23.1 ± 2.7
Lymph volume (mL)	19.9 ± 3.0	17.5 ± 1.6

[1)]Means ± SD, n = 5.
*Significantly different from controls ($p < 0.05$).

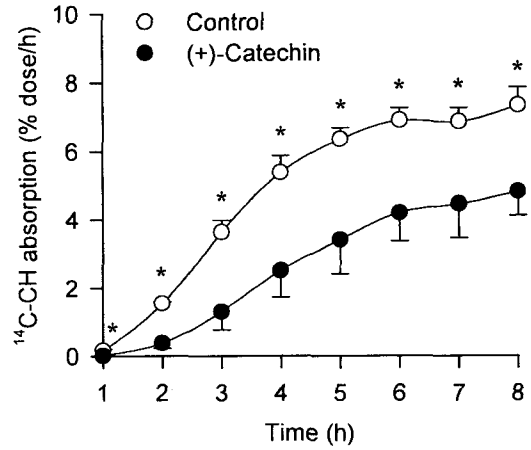

Fig. 2. Hourly rates of lymphatic ^{14}C-cholesterol (^{14}C-CH) absorption in rats infused with (+)-catechin. Values are expressed as means ± SD, n = 5. Asterisks (*) denote significant differences between groups at each time interval ($p < 0.05$).

Table 3. Effect of (+)-catechin on the cumulative lymphatic ^{14}C-cholesterol absorption (%dose/8 h)

Time	Control[1)]	(+)-Catechin
1 h	0.16 ± 0.05	0.02 ± 0.01*
2 h	1.70 ± 0.10	0.40 ± 0.15*
3 h	5.34 ± 0.39	1.71 ± 0.65*
4 h	10.74 ± 0.72	4.23 ± 1.41*
5 h	17.09 ± 0.92	7.67 ± 2.37*
6 h	24.01 ± 0.98	11.86 ± 3.18*
7 h	30.88 ± 1.00	16.32 ± 3.27*
8 h	38.22 ± 1.22	21.14 ± 3.56*

[1)]Means ± SD, n = 5.
*Significantly different from controls ($p < 0.05$).

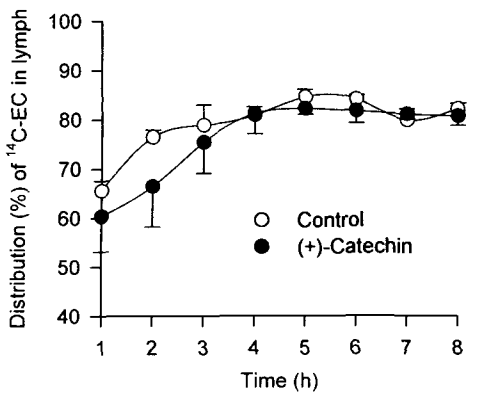

Fig. 3. Percent (%) distribution of ^{14}C-radioactivity in esterified cholesterol (^{14}C-EC) of lymph in rats infused with (+)-catechin. Values are expressed as means ± SD, n = 5.

fused with (+)-catechin than in controls. The rates of total cholesterol output were 1.4 ± 0.2 μmol/h in rats infused with (+)-catechin and 1.70 ± 0.18 μmol/h in controls. The cumulative lymphatic output of total cholesterol was significantly decreased in rats infused with (+)-catechin (Table 2).

Lymphatic outputs of α-tocopherol and other lipids

During lipid infusion, the hourly rates of α-tocopherol absorption were significantly lower in rats infused with (+)-catechin than in control rats (Fig. 4, $p < 0.05$). The average rates of α-tocopherol absorption for 8 h were 3.03 ± 0.38% dose/h (107.1 ± 13.3 nmol/h) in rats infused with (+)-catechin and 4.03 ± 0.28% dose/h (142.6 ± 9.5 nmol/h) in controls. The cumulative amount of α-tocopherol for 8 h also was significantly decreased in rats infused with (+)-catechin (Table 2).

However, (+)-catechin infusion did not affect the hourly

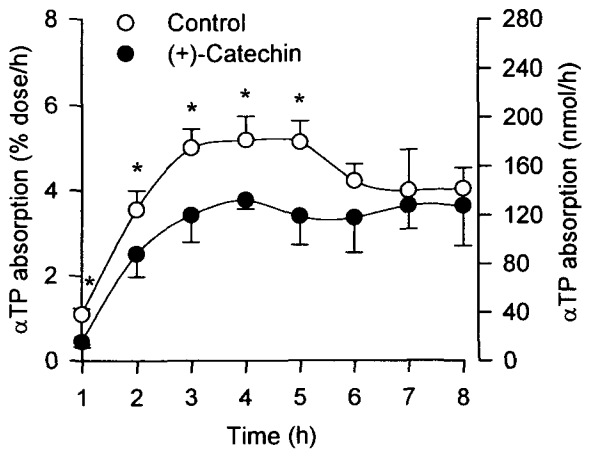

Fig. 4. Hourly rates of lymphatic α-tocopherol (αTP) absorption in rats infused with (+)-catechin. Values are expressed as means ± SD, n = 5. Asterisks (*) denote significant differences between groups at each time interval ($p < 0.05$).

rates of oleic acid, other fatty acids, and phospholipid outputs (Table 2). No significant differences were noted in the cumulative lymphatic outputs of these lipids between groups.

DISCUSSION

The results of this study provide the first evidence that intraduodenal infusion of (+)-catechin significantly lowers the absorption of cholesterol in rats, whereas it does not affect the outputs of fats such as oleic acid and phospholipid. Data show that the % distribution of labeled cholesterol appearing in lymph was not affected by the (+)-catechin infusion, indicating that the inhibition of cholesterol absorption by (+)-catechin is not associated with inhibition of cholesterol esterification within the enterocyte. This study indicates that (+)-catechin selectively inhibits the intestinal absorption of cholesterol, suggesting that (+)-catechin may be used as an effective means of inhibiting the absorption of cholesterol.

At present, the exact mechanism whereby (+)-catechin lowers the intestinal absorption of cholesterol is far from clear. However, we recently showed that green tea catechins, which have a structural similarity to (+)-catechin, significantly lower the absorption of cholesterol in rats under *in vivo* conditions (20). The cholesterol absorption was dose-dependently decreased with increasing amounts of green tea extract standardized at 42.9 mg and 120.5 mg of total catechins. Also, we observed that tea catechins inhibit pancreatic PLA_2 activity under *in vitro* and *in vivo* conditions (19). The inhibition (%) of PLA_2 by the major tea catechins, epigallocatechin gallate (EGCG), (-)-epigallocatechin, (-)-epicatechin gallate, (+)-catechin, and (-)-epicatechin were 64.9, 39.7, 25.7, 24.8 and 23.3%, respectively, indicating that EGCG is most effective in inhibiting PLA_2 activity. Furthermore, intraduodenal infusion of EGCG, along with a lipid emulsion containing ^{14}C-phosphatidylcholine (PC), markedly decreased the amount of ^{14}C-radioactivity appearing into the lymph, whereas it significantly increased the amount of unhydrolyzed PC remaining in the intestinal lumen (32). This observation is of particular significance in view of the emerging evidence that the initial hydrolysis of the surface PC of a lipid emulsion to lysophosphatidylcholine (lysoPC) is required for efficient hydrolysis of core triacylglycerol by pancreatic lipase/colipase and for stimulation of cholesterol uptake (33,34). The presence of PC on the surface of lipid emulsion slows the hydrolysis of the core triacylglycerol by pancreatic lipase/colipase, whereas an initial hydrolysis of PC to lysoPC by pancreatic PLA_2 facilitates the binding of lipiase/colipase to the substrate interface, resulting in a rapid hydrolysis of triacylglycerol to fatty acids and

monoacylglycerol (33-35). Thus, the combined action of pancreatic PLA_2 and lipase/colipase is critical for supporting the normal rates of luminal hydrolysis and absorption of lipids including cholesterol. Evidence also shows that flavonoids such as hesperetin and myricetin, which are also structurally similar to (+)-catechin, are potent inhibitors of pancreatic PLA_2 (18). Based on the above-cited observations, it is probable that luminal (+)-catechin inhibits pancreatic PLA_2 activity, slowing luminal digestion of lipids and formation of mixed micelles, thereby lowering the absorption of cholesterol.

The present data show that the lymphatic output of phospholipid remained unaffected. This observation is consistent with our recent finding (29) that enteral infusion of PC inhibits the absorption of cholesterol without affecting phospholipid output. It is known that lysoPC, once taken up by the enterocyte, is hydrolyzed to fatty acid and glycerol-3-phosphocholine (36-38). Much of the fatty acid is incorporated into triglyceride within the enterocyte, and glycerol-3-phosphocholine is transported via the portal vein into the liver for further metabolism. Thus, the amount of phospholipid appearing into the lymph does not necessarily represent the luminal availability of phospholipid since the enterocyte can regulate the intracellular phospholipid depending on the cellular demand for phospholipid during chylomicron synthesis (36-40).

Our data indicate that (+)-catechin also significantly lowers the intestinal absorption of α-tocopherol, whereas, under the same experimental conditions, the lymphatic output of oleic acid, as infused in the form of triolein, is not affected. This observation is consistent with our earlier finding (32) that luminal infusion of (+)-catechin inhibits the absorption of α-tocopherol, but not of retinol. The exact mechanism underlying the differential effect of (+)-catechin on these lipids is currently unknown. However, our recent finding showed that addition of PC in a triolein emulsion increases the lymphatic output of oleic acid, whereas it inhibits the absorption of both cholesterol and α-tocopherol and that substitution of lysoPC for PC enhances their absorptions in rats (41). Similarly, it has been shown in vitro that micellar PC does not interfere with the cell uptake of relatively less hydrophobic lipids such as retinol and fatty acid (oleic acid), whereas it inhibits the uptake of cholesterol (33,42). Thus, it is postulated that extremely hydrophobic lipids such as cholesterol and α-tocopherol are transferred at much slower rates from PC micellar matrix to the enterocyte than oleic acid or retinol, and less readily available for uptake by the enterocyte.

In the present study, 200 mg (+)-catechin was infused for 8 h. This amount is equivalent to 0.60 mg/kJ on the basis of the rat's daily food intake of 20 g providing 334 kJ (AIN-93G diet). For humans consuming 8,360 kJ (2,000 kcal)/d, the amount of (+)-catechin infused in this study would correspond to a daily intake of 5.0 g catechins. In a clinical trial designed to determine toxicity of green tea extract or catechins, a daily dose of up to 6.6 g was shown to be well-tolerated over 6 months in humans (43). However, our present data indicate that (+)-catechin may adversely affect the nutritional status of α-tocopherol due to its inhibitory effect on its intestinal absorption. Further studies are needed to determine whether chronic intake of (+)-catechin influences the body or nutritional status of vitamin E and the overall status of antioxidant defense system, since (+)-catechin itself exhibits strong antioxidant properties (11,12).

In summary, our data here clearly show that (+)-catechin, a flavonoid present in a wide variety of fruit and vegetables and tea, is a potent inhibitor of the intestinal absorption of cholesterol. Further studies are needed to answer the question of whether (+)-catechin lowers the intestinal absorption of cholesterol in humans. Also, studies are warranted to determine the effects of (+)-catechin or other bioactive flavonoids on pancreatic lipase and PLA_2 activity and lipid metabolism.

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