



Review Article

Green tea and type 2 diabetes

Jae-Hyung Park, Jae-Hoon Bae, Sung-Soon Im, Dae-Kyu Song*

Department of Physiology, Keimyung University School of Medicine, Daegu, Korea

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ABSTRACT

Green tea and coffee consumption have been widely popular worldwide. These beverages contain caffeine to activate the central nervous system by adenosine receptor blockade, and due to the caffeine, addiction or tolerance may occur. In addition to this caffeine effect, green tea and coffee consumption have always been at the center of discussions about human health, disease, and longevity. In particular, green tea catechins are involved in many biological activities such as antioxidation and modulation of various cellular lipid and proteins. Thus, they are beneficial against degenerative diseases, including obesity, cancer, cardiovascular diseases, and various inflammatory diseases. Some reports also suggest that daily consumption of tea catechins may help in controlling type 2 diabetes. However, other studies have reported that chronic consumption of green tea may result in hepatic failure, neuronal damage, and exacerbation of diabetes, suggesting that interindividual variations in the green tea effect are large. This review will focus on the effect of green tea catechins extracted from the *Camellia sinensis* plant on type 2 diabetes and obesity, and the possible mechanistic explanation for the experimental results mainly from our laboratory. It is hoped that green tea can be consumed in a suitable manner as a supplement to prevent the development of type 2 diabetes and obesity.

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1. Introduction

Green tea is now consumed everywhere as a beverage and is a remedy to prevent some degenerative diseases. However, the effectiveness of green tea consumption on diseases has not been clearly demonstrated in humans, although many animal experiments have shown positive results. Green tea extract (GTE) has many naturally occurring biological components of which polyphenolic epicatechins (ECs) are predominantly active (Fig. 1). These include (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), and (-)-EC. The EC and EGC are catechol catechins, EGC

and EGCG are pyrogallol catechins, and ECG and EGCG are galate catechins. This review focuses on the effect of EGCG on diabetes and obesity. The first section describes the overall effect of EGCG on diabetes and obesity, and the second part is an analysis of the effect of EGCG on degenerative metabolic diseases.

2. Overall conception of the effect of EGCG on diabetes and obesity

Daily consumption of green tea by patients with diabetes for several months is ineffective for ameliorating

* Corresponding author. Department of Physiology, Keimyung University School of Medicine, 1095 Dalgubeoldae-Ro, Dalseo-Gu, Daegu 704-701, Korea.

E-mail address: dk-song@kmu.ac.kr (D.-K. Song).

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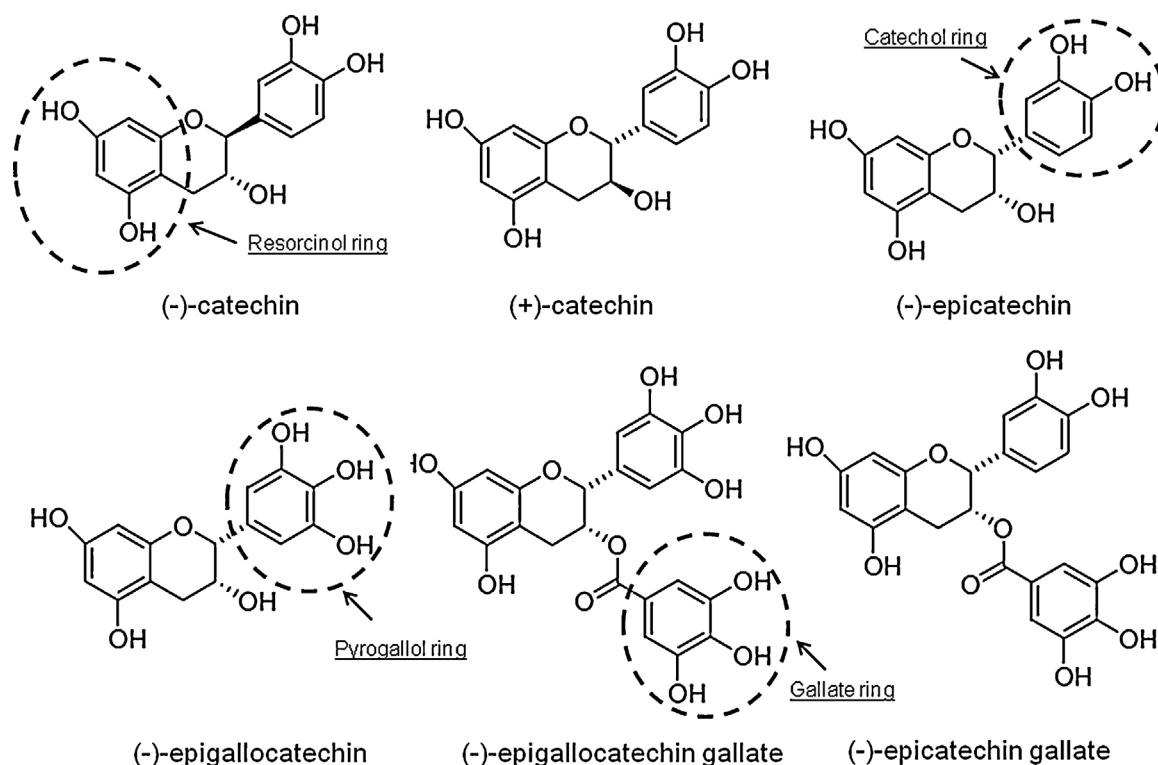


Fig. 1 – Naturally occurring catechins extracted from green tea.

diabetes-related parameters, including blood glucose levels, HbA1C levels, insulin resistance, and inflammation markers.¹ Many randomized trials^{2–6} support this result of Fukino et al.¹ However, some retrospective cohort studies in Japan⁷ and Taiwan⁸ suggest that green tea is effective against type 2 diabetes.

Those studies revealed that EGCG, the most abundant form of catechin in green tea, inhibits adipocyte proliferation and differentiation,^{9–11} increases cellular defense against oxidative stress,¹² and blocks sodium-dependent glucose transporter 1 (SGLT1)¹³ and lipid micelle formation¹⁴ in the intestine. However, the concentrations of EGCG required to decrease the number of preadipocytes and adipocytes are too high to be consumed by humans without considerable side effects.^{15–17} Although green tea catechins have the molecular structure to scavenge oxygen-free radicals, their effectiveness in biological systems has not been clarified. Some reports demonstrate that EGCG is a pro-oxidant and harmful for beta-cell survival in streptozotocin-induced diabetic rats.¹⁸ Blockage of SGLT1 and lipid micelle formation is the most important and strongest mechanism for gallate catechins to exert their effects against obesity and diabetes. However, there is a limitation to use gallate catechins as a remedy for these two metabolic diseases. A lower concentration of gallate catechins than those that block SGLT1 blocks sodium-independent glucose transporters (GLUTs) in various tissues. Although dietary glucose absorption into the circulation is mainly performed by intestinal SGLT1 as well as by some GLUTs, cellular glucose uptake as an energy source in most cells is performed by insulin-dependent (GLUT4) and insulin-independent GLUTs. Maximum blood EGCG concentrations

are achieved 90 minutes after green tea ingestion and considerable concentrations of EGCG are present in circulation for 3–4 hours. This means that the effects of EGCG in the alimentary tract remain only for 1 hour, but the effects in circulation remain for several hours. Blocking cellular glucose uptake during the postprandial period resembles insulin resistance, eventually leading to failure of beta cells to secrete more insulin.

The discrepancy among human epidemiological data for the antidiabetic effects of green tea catechins can be attributed to several reasons. As shown in Table 1, one cup of green tea contains approximately 100 mg EGCG in 1 g GTE. This quantity easily makes blood concentrations of EGCG about 100 nM in a fasting state, and a concentration that can inhibit various GLUTs. In addition, there are significant interindividual variations in blood concentrations of EGCG after green tea ingestion,^{19,20} suggesting that there are difficulties in

Table 1 – Species variation in the amount of EGCG to be absorbed into circulation after IG ingestion of EGCG*

| | IG ingestion of EGCG | Blood concentrations | Refs |
|-------|----------------------|----------------------|------|
| Rat | 75 mg/kg | 35nM | 21 |
| Mouse | 75 mg/kg | 280nM | 22 |
| Human | 2 mg/kg | 170nM | 20 |
| | 525 mg in GTE/man | 4.4 μM | 19 |

* A cup of green tea contains approximately 100 mg EGCG in 1 g GTE. EGCG, (-)-epigallocatechin-3-gallate; GTE, green tea extract; IG, intragastric.

controlling EGCG concentration in experiments involving humans, as the meals make absorption of the GTE slower. By contrast, animal experiments are more controllable and show that rats²¹ have the lowest oral bioavailability of EGCG compared with mice²² and humans (Table 1); in fact, the oral bioavailability of EGCG is lower in mice than that in humans. Therefore, during animal experiments, oral ingestion of GTE or EGCG only shows the intestinal effects but not the effect in circulation. Thus, the results may be more interpreted as positive results against obesity and diabetes than those obtained from humans. Therefore, to extend the intestinal effects of EGCG and to decrease the circulatory effect of EGCG, entry of EGCG into circulation should be blocked, at least for using EGCG to treat type 2 diabetes and obesity.

3. EGCG effect in metabolic tissues

3.1. How much green tea should we take for the intestinal effect of EGCG?

Kobayashi et al¹³ found that the 50% inhibitory concentration (Ki) of ECG to block 50% of rabbit intestinal glucose uptake was 390 μ M. Park et al²³ reported that the 50% inhibition of glucose uptake was around 100 μ M for EGCG in the human colon adenocarcinoma CACO-2 cells, whereas an inhibitory effect was observed at 10 μ M. Concentrations of EGCG > 100 μ M are necessary to block lipid micelle formation.¹⁴ Raederstorff¹⁴ further found that 500-mg EGCG/kg body weight is necessary to inhibit 50% cholesterol absorption in rats. Park et al²⁴ reported that the EGCG effect can be potentiated if EGCG is applied as a constituent of an intact GTE, as other GTE constituents protect EGCG from degradation or ECG adds the same effect as EGCG. Use of GTE, not EGCG, is a means to reduce the amount of EGCG used. GTE containing at least 100 mg EGCG

may be necessary to exert an effect on SGLT1 and lipid micelle formation in the gastrointestinal tract.²³⁻²⁵ Fortunately, this level would not block amino acid and polypeptide transporters in the intestine.¹³ Therefore, it would be sufficient to have one cup of green tea just prior to a meal. However, as shown in Tables 1 and 2, plasma concentrations of EGCG could easily reach 100 nM with normal daily consumption of green tea, which is a concentration that would inhibit various GLUTs in tissues and lead to a shortage of glucose in cells. This is a burden on beta cells and glucose-deficient cells to decrease blood glucose levels during the postprandial period.

3.2. EGCG on oxidative stress

Cell viability is impaired significantly when preadipocytes are treated with 50 μ M EGCG, but recover by treatment with the antioxidant vitamin E.¹⁵ This means that this concentration of EGCG may act as a pro-oxidant.¹⁸ Low cell viability was not observed until the concentration of EGCG is 10 μ M. These phenomena are also true for mature adipocytes; when 50 μ M but not 10 μ M EGCG was applied for 4 days during the early 3T3-L1 adipocyte differentiation (Days 0-3) or during the maturation period (Days 4-7), cell viability and cellular triglyceride accumulation decreased, and intracellular reactive oxygen species (ROS) accumulation increased. This ROS accumulation caused by EGCG may be linked to the gallate moiety in the EGCG molecule, as catechin does not possess the gallate moiety and has no effect on intracellular ROS concentrations. At the concentration that EGCG increases intracellular ROS concentrations, the expression of peroxisome proliferator-activated receptor- γ is downregulated in mature adipocytes, correspondingly downregulating adiponectin.^{26,27} In addition, the expression of retinol binding protein-4 (RBP-4) is upregulated. The increased expression of RBP-4 due to 50 μ M EGCG was partially but not totally recovered by co-treatment

Table 2 – Dose-dependent effects of EGCG

| Functions | Concentrations, μ M | Refs | Catechins |
|-------------------------------------|-------------------------|------|----------------------------|
| SGLT1 block | >1 | 23 | <ECG |
| | | 13 | (only GC) |
| GLUTs block | <1 | 24 | <ECG |
| | | 39 | (only GC) |
| | | 16 | |
| | | 40 | |
| Micelle formation block | >100 | 14 | \approx ECG (probably) |
| Alcohol absorption block | >100 | 23 | \approx ECG (only GC) |
| In K_{ATP} channels | | | |
| PIPs sensitivity block | <1 | 48 | only EGCG |
| ATP sensitivity block | >1 | 48 | only EGCG |
| Direct channel block | >10 | 46 | >EGC, <ECG |
| In adipocytes | | | |
| Increased RBP-4 secretion | >1 | 15 | >EGC |
| Increased ROS generation | >10 | 15 | >EGC |
| Decreased adipocyte survival | >10 | 15 | >EGC |
| Decreased PPAR- γ expression | >10 | 15 | >EGC |
| Decreased adiponectin expression | >10 | 15 | >EGC |

ATP, adenosine triphosphate; ECG, (-)-epicatechin-3-gallate; EGC, (-)-epigallocatechin; EGCG, (-)-epigallocatechin-3-gallate; GC, gallatecatechin; GLUTs, glucose transporters; K_{ATP} , ATP-sensitive K^+ ; PIPs, phosphatidylinositol polyphosphates; PPAR- γ , peroxisome proliferator-activated receptor- γ ; RBP-4, retinol binding protein-4; ROS, reactive oxygen species; SGLT1, sodium-dependent glucose transporter 1.

with vitamin E and EGCG, suggesting that increased ROS generation could be a factor for EGCG-induced RBP-4 upregulation. The increased expression of RBP-4 after EGCG treatment was further recovered by co-treatment of methyl pyruvate with vitamin E, which is a cellular energy source bypassing GLUTs and glycolysis, suggesting that impaired glucose uptake by EGCG was also a causative mechanism for RBP-4 upregulation. Secretion of RBP-4 in human adipocytes consistently increased with 10 μM EGCG, which is lower than the 50 μM EGCG required to induce intracellular ROS accumulation. This observation suggests that the ROS-independent mechanism to block glucose uptake can be another critical factor to increase RBP-4 expression and secretion. Thus, long-term application of lower EGCG concentrations could increase RBP-4 signaling. The EGCG concentration dependency of intracellular ROS accumulation in adipocytes in our study was consistent with other findings.^{9,11,28,29} Unfortunately, EGCG-induced ROS generation at the higher EGCG concentration does not show tissue specificity.^{17,30–32} If it was tissue specific, it would be useful for obesity to target only adipocytes or for certain localized cancers. In addition, higher concentrations of EGCG are not achievable in human plasma without considerable adverse effects.³³ Therefore, the pro-oxidative nature of high concentrations of EGCG is not an acceptable mechanism to protect against obesity and even cancers. There are reports³⁴ describing EGCG concentration dependency in the EGCG–oxidative stress relationship; nanomolar concentrations of EGCG have an antioxidant action and micromolar concentrations of EGCG have a pro-oxidant action. However, the pro-oxidative activity of EGCG can occur at concentrations < 50 μM , even at about 1 μM concentration in the beta cells damaged previously by streptozotocin¹⁸ or hippocampal neuronal cells.¹⁷ This suggests that EGCG always induces ROS stress in cells that would not occur if the cell's scavenging systems are intact. Therefore, EGCG action against oxygen-free radicals may be altered by the kinds of radical stimulants, cellular conditions, and the exposed time to EGCG. Green tea catechins can exert their effect as both pro-oxidants and antioxidants;^{12,35} the presence of the gallate (G) ring, the catechol (C) ring, the pyrogallol (P) ring, or the resorcinol (R) ring is important for the antioxidant activities of catechins¹² (Fig. 1). In addition, the P ring is also important for the antifungal action of catechins.³⁶ The pro-oxidative activity of catechins is attributed to their potency from auto-oxidation and peroxidase-catalyzed oxidation.³⁷ As previously noted, the potency of increasing ROS in adipocytes is EGCG > ECG, but not nongallate catechins, of which EGCG has both pyrogallol and gallate moieties.

3.3. EGCG on cellular glucose uptake

We think that a critical factor to increase RBP-4 secretory signaling from mature adipocytes is the effect of EGCG to decrease cellular glucose uptake. It is well known that cellular glucose uptake in various tissues is impaired in the insulin-resistance state, making beta cells secrete more insulin and causing early beta-cell exhaustion throughout life. Impaired glucose uptake by EGCG can be observed at EGCG concentrations < 10 μM .³⁸ Park et al²⁴ also showed that EGCG inhibits cellular glucose uptake at 100 nM in myocytes, adipocytes, and

beta cells, and 1 μM in hepatocytes, which is easily achievable in human plasma by oral intake of two to three cups of green tea²⁴ (Table 1). These findings are consistent with the results obtained in other tissues by previous observations,^{16,39,40} suggesting that most tissues possessing either of various GLUTs can be hindered with glucose use in the presence of EGCG. The adipokine RBP-4 is secreted from mature adipocytes when adipocytes detect deficient glucose uptake.⁴¹ In the fasting state, secretion of RBP-4 stimulates hepatic glucose output and inhibits muscular glucose uptake,⁴² probably to spare blood glucose levels. Therefore, abnormally increased expression and secretion of RBP-4 may elicit insulin resistance. It would be difficult to normalize blood glucose levels by insulin during the postprandial period if plasma EGCG hinders most tissues to uptake glucose. This action of EGCG on GLUTs may be related to its gallate moiety, because ECG and genistein also have a blocking effect toward GLUTs, and ECG is the more potent.^{31,39} The mechanism of EGCG to inhibit cellular glucose uptake may be either blockade of insulin signaling or direct competition with glucose for GLUTs.^{16,43} We found that insulin-induced Ser473 phosphorylation of protein kinase B remained unchanged in the presence of EGCG in hepatocytes, adipocytes, myocytes, and beta cells.²⁴ The impact of this EGCG action on cellular glucose uptake can be observed *in vivo* and we found that EGCG at about 1 μM in blood acutely elevates blood glucose and insulin levels during the oral glucose tolerance test (OGTT) in humans.²⁴ It confirms that daily intake of green tea is clinically relevant. We orally applied GTE-containing EGCG at about 100 mg to selected human participants either immediately or 1 hour prior to oral glucose ingestion for the OGTT. In the former case, blood glucose levels during the OGTT were maintained lower than the control without GTE ingestion. However, in the latter, blood glucose and insulin levels were greater than those in the control. In addition, greater insulin resistance was observed during the insulin tolerance test. This finding was also true for ECG, and a gallate catechin-free GTE would not exert this effect. This result clearly suggests that absorbed gallate catechins, mainly EGCG and ECG, hinder cellular glucose uptake in insulin-sensitive tissues during the OGTT and thus increase insulin secretion from beta cells. This phenomenon occurring by ingesting the GTE is well matched with the postprandial period in prediabetes with insulin resistance and overt type 2 diabetes. We further confirmed that this EGCG action was not associated with the effect of EGCG on adenosine triphosphate (ATP)-sensitive K^+ (K_{ATP}) channels because it occurred even in K_{ATP} channel-deficient mice.

3.4. Direct K_{ATP} channel modulation of EGCG

The plasmalemmal K_{ATP} channel is an octamer that includes four inwardly rectifying potassium (Kir)6.2 and four sulfonylurea receptors (SURs). EGCG inhibits the activity of Kir6.2/SUR1 (beta-cell type) in *Xenopus* oocytes expressing K_{ATP} channels, with an inhibitory concentration 50 (IC_{50}) of about 140 μM , which is also observed in Kir6.2/SUR2A (cardiac type) and Kir6.2/SUR2B (vascular type). The inhibitory potency of EGCG was similar to the IC_{50} of EGCG for voltage-dependent potassium (Kv) 1.5 channels (101 μM).⁴⁴ ECG is three times more effective for this inhibition than EGCG, and nongallate

catechins did not have any effect. The IC_{50} of EGCG for channel inhibition was about $20 \mu\text{M}$ with Kir6.2 Δ C36 channels, which are the channel pore-forming subunits. The absence of the SUR subunits suggests that the regulatory subunit SUR may hinder the inhibitory action of EGCG on Kir6.2. The principal mechanism for Kir6.2 blockade of gallate catechins may be due to the interaction between EGCG and ECG with lipid bilayers embedded in the K_{ATP} channels, because the interaction of catechins with lipids is stronger when the catechol ring and gallate ring are both present as in ECG.⁴⁵ A small contribution of the pyrogallol ring is also detected⁴⁵ because EGC can inhibit K_{ATP} channels, but only slightly.⁴⁶

3.5. EGCG-induced change in K_{ATP} channel sensitivity to phosphatidylinositol polyphosphates and ATP

The K_{ATP} channel activity is inhibited by ATP through the Kir6.2 subunit and activated by MgADP through the SUR subunit.⁴⁷ Phosphatidylinositol polyphosphates (PIPs) such as PIP2 and PIP3 activate the channel through the Kir6.2. The K_{ATP} channels play crucial roles in glucose-stimulated insulin secretion in beta cells and protect cardiac myocytes from metabolic inhibition. Although direct K_{ATP} channel inhibition was accomplished by gallate catechins such as EGCG and ECG, the reducing effect of the GTE on K_{ATP} channel ATP and PIP sensitivity only occurred in EGCG, which additionally has the hydroxyl group (-OH) on the pyrogallol moiety.⁴⁸ The ATP sensitivity of the K_{ATP} channel in the presence of $10 \mu\text{M}$ EGCG was 10 times less than that in the absence of EGCG ($13.4 \mu\text{M}$ vs. $120 \mu\text{M}$). EGCG did not eliminate the bound ATP molecules from the channels but inhibited channel binding of ATP. The adenosine monophosphate (AMP) and adenosine diphosphate blocks for K_{ATP} channels were not hindered by EGCG. The γ -phosphate tail of ATP is bound to R50 in the N terminal of Kir6.2, and ATP binding to Kir6.2 is facilitated by incorporating SUR1. Our results show that EGCG may inhibit the

Table 3 – Structure–function relationships of green tea catechins

| Functions | Structures | Refs |
|--------------------------|------------------------------------|------|
| SGLT1 block | G ring | |
| GLUTs block | G ring | |
| Alcohol absorption block | G ring | |
| In K_{ATP} channels | | |
| PIP sensitivity block | G ring + P ring | |
| ATP sensitivity block | G ring + P ring | |
| Direct channel block | G ring + C ring > G ring + P ring | |
| ROS generation | G ring + P ring > G ring + C ring | |
| ROS scavenging | G ring, C ring, P ring, and R ring | 12 |
| Antifungal action | P ring | 36 |

ATP, adenosine triphosphate; C ring, catechol ring; G ring, gallate ring; GLUTs, glucose transporters; K_{ATP} , ATP-sensitive K^+ ; P ring, pyrogallol ring; PIPs, phosphatidylinositol polyphosphates; R ring, resorcinol ring; ROS, reactive oxygen species; SGLT1, sodium-dependent glucose transporter 1.

facilitating function of SUR1. Moreover, the decrease in the channel PIP sensitivity caused by EGCG appears even at $1 \mu\text{M}$ EGCG. This may have occurred due to direct hindrance of the PIP interactions with their binding sites on Kir6.2 by EGCG. The mechanism may be due to the negative charges of EGCG and the positive charges on the PIPs binding sites of the channels against the negative charges of PIPs. It would require a serious involvement of EGCG in K_{ATP} channel gating kinetics if the two major modulators ATP and PIPs have a limitation to play their actions.

4. Concluding remarks and future perspectives

The effects of EGCG regarding diabetes and obesity are summarized in Table 2 and the related molecular structures of

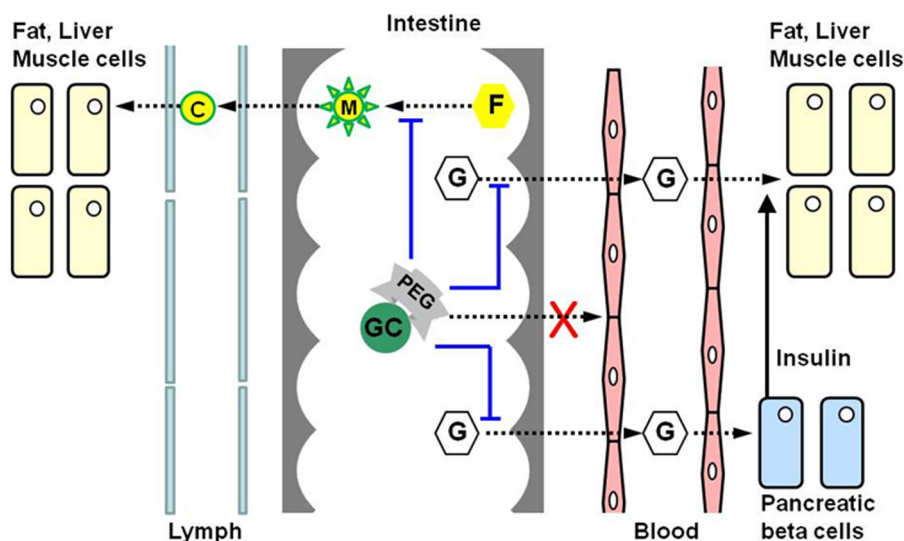


Fig. 2 – Schematic representation of gallated catechins inhibiting glucose uptake and micelle formation. Polyethylene glycol-3350 or poly- γ -glutamate blocks absorption of gallate catechins into circulation. Broken lines represent movement of the molecules; unbroken arrow line represents facilitation by insulin; unbroken block lines represent inhibition by GC. C, chylomicron; F, dietary fat; G, glucose; GC, gallate catechins; M, micelle.

EGCG are shown in Table 3. The antioxidative effects of green tea can be a substitute for other well-known antioxidants. Blockage of adipocyte differentiation and proliferation by EGCG is not possible in humans because intolerable plasma concentrations of EGCG are required. Animal data considering the effect of EGCG on obesity and diabetes cannot be replicated in humans because of different oral bioavailability among species. Green tea intake to exert beneficial intestinal effects sufficiently elevates blood EGCG levels to inhibit cellular glucose uptake. Many previous *in vitro* experimental data show the downstream phenomena for the effect of EGCG on inhibiting cellular glucose uptake, such as elevated AMP-activated protein kinase activity. EGCG may be effective for cancer protection due to its inhibitory action on cancer-cell glucose utilization, but not by direct modulation of specific cellular signaling. Blocking the absorption of green tea gallate catechins, which block cellular glucose uptake in the circulation, may be a clue for green tea use against diabetes and obesity. This also means prolongation of their effects in the intestine. Polyethylene glycol-3350 or poly- γ -glutamate dramatically and selectively block entry of gallate catechins into circulation, prolonging their intestinal effects (Fig. 2).^{23–25} Human clinical trials should proceed to develop a safer treatment tool against type 2 diabetes and related obesity.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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