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Review

Mechanisms of hypolipidemic and anti-obesity effects of tea and tea polyphenols

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Among the health-promoting effects of tea and tea polyphenols, the cancer-chemopreventive effects in various animal model systems have been intensively investigated; meanwhile, the hypolipidemic and antiobesity effects in animals and humans have also become a hot issue for molecular nutrition and food research. It has been demonstrated that the body weights of rats and their plasma triglyceride, cholesterol, and LDL-cholesterol have been significantly reduced by feedings of oolong, black, pu-erh, and green tea leaves to the animals. It has been suggested that the inhibition of growth and suppression of lipogenesis in MCF-7 breast cancer cells may be through down-regulation of fatty acid synthase gene expression in the nucleus and stimulation of cell energy expenditure in the mitochondria. The experimental data indicated that the molecular mechanisms of fatty acid synthase gene suppression by tea polyphenols (EGCG, theaflavins) may invite down-regulation of EGFR/PI3K/Akt/Sp-1 signal transduction pathways.

Keywords: Catechins / Fatty acid synthase / Tea / Tea polyphenols / Theaflavins

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1 Introduction

During the last decade, the health-promoting effects of tea and tea polyphenols have been intensively investigated. The hypolipidemic and antiobesity effects in animals and humans have become an important issue for molecular nutrition and food research. A brief review on this interesting field has been suggested. The scope of this review will be confined to the biochemical aspects of the lipogenic enzyme fatty acid synthase (FAS), which has been shown to be suppressed by tea and tea polyphenols.

Tea is one of the most popular beverages consumed worldwide. Quantitatively, it is next only to water and well ahead of coffee, beer, wine, and carbonated soft drinks [1, 2]. It can be categorized into four types, depending on the level of fermentation, namely green (unfermented), oolong (partially fermented), black (completely fermented), and pu-erh (drastically fermented and aged) teas. The tea that originated from the plant *Camellia sinensis* is consumed in different parts of the world as green, oolong, black, or pu-erh tea. Green and oolong teas are favored in Oriental countries, while black tea is favored in Western countries, and oolong tea and pu-erh tea are consumed mostly in China [3, 4].

In general, green tea has been found to possess higher antioxidant activity owing to the higher content of catechins [5]. The processes used in the manufacture of black and pu-erh teas are known to decrease levels of the monomeric catechins to a much greater extent of polymerization that leads to the formation of theaflavins and thearubigins. The production and consumption of the partially fermented oolong tea and drastically fermented pu-erh tea are confined to China. All teas are not created equally. Green tea, oolong tea, black tea, and pu-erh tea are processed differently during manufacturing. To produce green tea, freshly plucked tea leaves are steamed to prevent fermentation, yielding a dry, stable product [3]. Catechins (Fig. 1) are the main compounds in green tea; they consist of (−)-epicatechin (EC), (−)-epicatechin-3-gallate (ECG), (−)-epigallo-

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Abbreviations: EC, epicatechin; **ECG**, epicatechin-3-gallate; **EE**, energy expenditure; **EGC**, epigallocatechin; **EGCG**, (−)-epigallocatechin-3-gallate; **EGF**, epidermal growth factor; **FAS,** fatty acid synthase; **GLUT 4**, glucose transporter 4; **NF-κB**, nuclear factor-κB; **PI3K**, phosphatidylinositol-3-kinase; **PPARs**, peroxisome proliferator-activated receptors; **TF-1**, theaflavin; **TF-2b**, theaflavin-3′-gallate; **TF-3**, theaflavin-3,3′-digallate

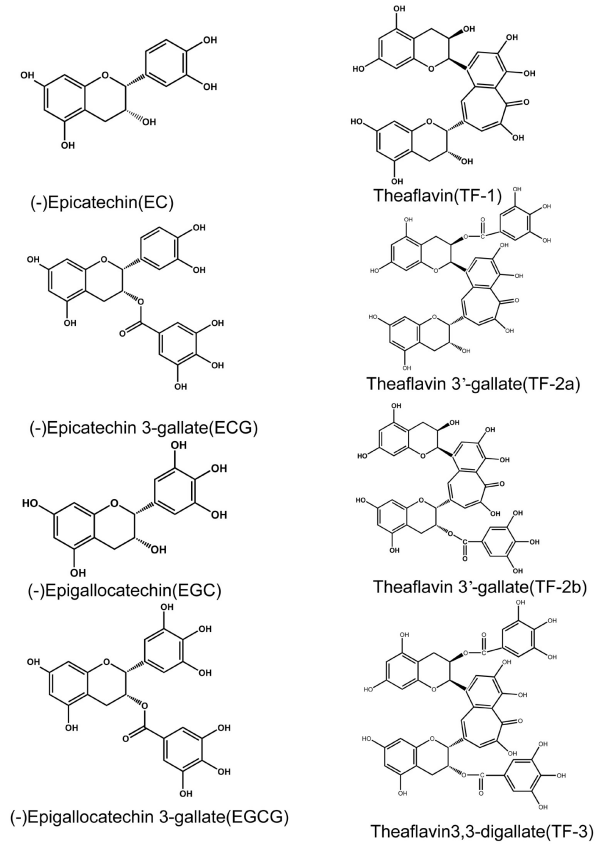

Figure 1. Chemical structures of tea polyphenols green tea catechins including EC, ECG, EGC, and EGCG. Black tea theaflavins including TF-1, TF-2a, TF-2b, and TF-3.

catechin (EGC), and (−)-epigallocatechin-3-gallate (EGCG). To produce oolong, black, and pu-erh teas, the fresh tea leaves are allowed to wither, decreasing their moisture content until their weight approached appropriate percentage (this value is assessed by expertise experience) of the original leaf weight. The withered leaves are then rolled and crushed, initiating the fermentation of polyphenols. This fermentation process converts catechins to theaflavins, namely theaflavin (TF-1), theaflavin-3-gallate (TF-2a), theaflavin-3′-gallate (TF-2b), and theaflavin-3,3′-digallate (TF-3) (Fig. 1), and thearubigins, consequently decreasing the catechin content.

It is obvious that excess body weight is a major health problem in most developed nations and is increasing in both prevalence and severity [6]. Obesity is a major risk factor for cardiovascular disease, diabetes, and cancer, for which the social costs are incalculable. Development of drugs to treat obesity or implementation of a dietary regimen to prevent obesity is a public health goal [7]. Obesity has increased at an alarming rate in recent years and is now a worldwide health problem.

It has been known for some time that tea helps to control obesity, and this is a common belief in Chinese society. Obese people are seldom found in the long-term tea-drinking individuals group [1]. Moreover, it is generally accepted that drinking tea for a long time will keep one living long to stay in good shape without becoming too fat and too heavy.

Based on biochemical and pharmacological studies, the mechanisms of action of tea in preventing obesity may be through stimulating hepatic lipid metabolism [8], inhibiting gastric and pancreatic lipases [9], stimulating thermogenesis [10, 11], modulating appetite [12], synergism with caffeine and theanine [13], and finally suppressing FAS [7].

2 Inhibition of the body weight of rodents by tea and tea polyphenols

In 1998, a significant hypolipidemic and growth-suppressive effects of green tea leaves in rats after 63 wk of feeding were observed in our laboratory [14]. Recently, further comparative studies on the hypolipidemic and growth-suppressive effects of oolong, black, pu-erh, and green tea leaves in rats were carried out in our laboratory [1]. The body weights of rats were examined when 5–wk-old male Sprague-Dawley rats were fed the basal diet, 1.5 and 4% green, oolong, black, and pu-erh tea leaves. At 30 wk, feeding 1.5% green tea leaves had produced no reduction in body weight, but 1.5% oolong tea ($p < 0.01$), black tea ($p < 0.05$), and pu-erh tea ($p < 0.005$) had remarkably decreased in the body weight as compared to the basal diet-fed group. In the feeding of 4% tea leaves, the rats were all remarkably reduced in body weight. At 30 wk, the body weights of green tea-fed was about 6% ($p < 0.005$), oolong tea-fed was 11% ($p < 0.001$), black tea-fed was about 7% ($p < 0.001$), and pu-erh tea-fed was about 13% ($p < 0.005$) lower than that of basal diet-fed [1]. It is interesting to note that the diet intakes among these five groups are not much different.

The effects of purified tea catechins on the body weights of rats were investigated by Kao *et al.* [15]. Intraperitoneal injection of EGCG, but not other structurally related catechins, such as EC, EGC, and ECG, caused acute body weight loss in Sprague–Dawley male and female rats within 2–7 days of treatment. In male rats, the effect of EGCG on body weight was dose-dependent. Female rats injected daily i.p. with 12.5 mg EGCG (*ca*. 92 mg/1 kg BW) lost 10% of their body weight relative to their initial weight and 29% relative to the control weight after 7 days of treatment [15].

Dietary supplementation with EGCG to mice significantly affected body weight development as demonstrated in a recent study [16]. EGCG dose-dependently reduced the body weight increase observed after feeding of a high-fat

diet. Control mice (male, New Zealand black) gained twice as much body weight during the 4-wk treatment as animals supplemented with 1% EGCG in the diet. This was not due to a decreased food intake since neither daily food intake nor total food intake during the treatment period was changed. The reduced body weight gain induced by EGCG was exclusively due to a reduction in body fat. Lean body mass development was not affected by EGCG [16]. Similar results on the beneficial effects of tea catechins on high-fat diet-induced obesity were observed by Murase *et al.* [8].

3 Suppression of plasma lipids by tea and tea polyphenols

The synthesis of fatty acid is the key step for lipogenesis, which is responsible for the complete synthesis of palmitate from acetyl CoA in the cytosol. In the rat, the pathway is well represented in adipose tissue and liver. In most mammals, glucose is the primary substrate for lipogenesis. Inhibition of lipogenesis occurs in type-I diabetes mellitus, and variations in its activity may affect the nature and extent of obesity [17].

The suppression of lipogenesis by oolong, black, pu-erh, and green tea leaves in rats has been demonstrated by the suppression of plasma triglyceride, cholesterol, and LDL-cholesterol in the experimental animals [1]. Pu-erh tea and oolon tea could lower the levels of triglyceride more significantly than those of green tea and black tea; meanwhile, pu-erh tea and green tea were more efficient than oolong tea and black tea in lowering the level of total cholesterol.

4 Inhibition of atherosclerosis in rodents by tea

A recent study on the first dose-response comparison of a green and black tea on normal hamsters after long-term supplementation and on a hamster model of atherosclerosis was reported [18]. Both teas were equally effective in inhibiting atherosclerosis with the lower dose (0.0625% tea solution) decreasing it by 26–40% and the high dose (1.25% tea solution) decreasing it by 46–63%. Atherosclerosis was inhibited by three mechanisms: hypolipidemic, antioxidant, and antifibrinolytic. There was a significant correlation between atherosclerosis and the three mechanisms [18].

Tea catechins (EC, EGC, ECG, and EGCG) dose-dependently inhibited the activity of pancreatic lipase. These results suggest that catechins with a galloyl moiety suppress postpyrandial hypertriacylglycerolemia by slowing down triacylglycerol absorption through the inhibition of pancreatic lipase in rats [19]. Because postpyrandial hypertriacylglycerolemia is a risk factor for coronary heart disease, these results suggest that catechins with a galloyl moiety may prevent this disease.

5 Inhibition of FAS *in vitro*

FAS is a key enzyme participating in energy metabolism *in vivo* [20] and is related to various human diseases such as obesity and cancer. Human cancer cells express high levels of FAS and inhibition of FAS is selectively cytotoxic to human cancer cells [21]. EGCG is an effective inhibitor of FAS from chicken liver *in vitro* [22]. Its inhibition of FAS is composed of reversible fast-binding inhibition, through which 52 μM EGCG can inhibit 50% of the activity of FAS. The marked inhibition of ketoacyl reduction shows that the inhibition is related to β-ketoacyl reductase of FAS. The observable protection of NADPH and competitive inhibition of NADPH for ketoacyl reduction indicate that EGCG may compete with NADPH for the same binding site.

To elucidate the structure-activity relationship of the inhibitory effects of tea polyphenols, the inhibition kinetics of the major catechins and analogs were investigated. Ungallated catechins from green tea do not show obvious inhibition compared with gallated catechins. Another gallated catechin, ECG, was also found as a potent inhibitor of FAS and its inhibition characteristics are similar to EGCG. Furthermore, the analogs of galloyl moiety without the catechin skeleton, such as propylgallate, also showed obvious slow-binding inhibition, whereas the green tea ungallated catechin did not [23]. Atomic orbital energy analyses suggest that the positive charge is more distinctly distributed on the carbon atom of ester bond of galloy moiety of gallate catechin, and that gallated forms are more susceptible for a nucleophilic attack than other catechins.

6 Suppression of FAS in cell culture

The *in vivo* suppression of FAS by tea and tea polyphenols has been demonstrated in the MCF-7 human breast carcinoma cells and HepG2 hepatocellular carcinoma cells [7, 24]. FAS is overexpressed in the malignant human breast carcinoma MCF-7 cells and its expression is further enhanced by epidermal growth factor (EGF). The EGF-induced expression of FAS was inhibited by green and black tea extracts (120 μg/mL). The expression of FAS was slightly stimulated by green, black, and oolong tea extracts at lower concentrations (30 μg/mL). The expression of FAS was also suppressed by the green tea polyphenol EGCG, but not catechin, EC, and EGC. Furthermore, the expression of FAS was significantly suppressed by TF-1, TF-2a, TF-2b, and TF-3at both protein and mRNA levels that may lead to the inhibition of cell lipogenesis and proliferation.

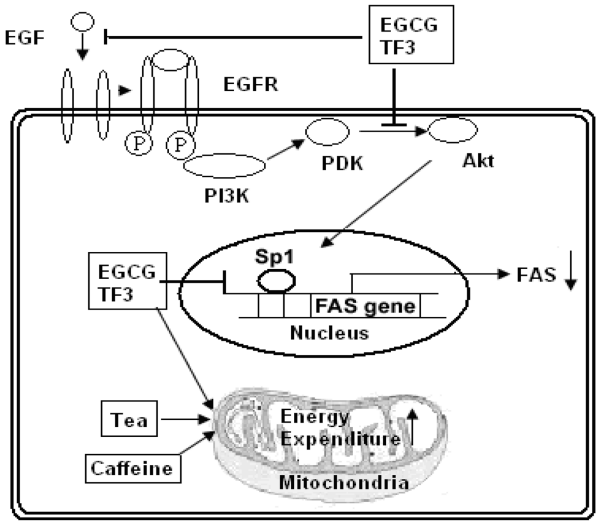

Figure 2. A proposed mechanism for the hypolipidemic and antiobesity effects of tea and tea polyphenols. In mitochondria: Tea and tea polyphenols stimulate the cellular energy expenditure that may reduce the body weight gain. Meanwhile, in the nucleus, the expression of FAS may be suppressed by tea and tea polyphenols through down-regulating EGF-receptor/PI3K/Akt/Sp-1 signal transduction pathway. This mechanism may inhibit the cellular lipogenesis and tissue growth. Tea polyphenols EGCG and TF-3 inhibit the growth factor EGF binding to EGFR, block the activation of the PI3K/Akt signal pathway, then reduce the DNA-binding capacity of nuclear transcription factor Sp-1, and finally lead to down-expression of FAS gene.

The PI3K (phosphatidylinositol-3-kinase) inhibitor LY294002 (5 μM) can block completely the FAS expression. Both EGCG and TF-3 inhibit the activation of Akt and block the binding of Sp-1 to its target site. Furthermore, the induced FAS protein was significantly suppressed by transient transfection of dominant negative Akt mutant gene into the MCF-7 cells. Additional experimental results demonstrated that the EGF-induced biosynthesis of lipids including triglyceride, cholesterol and fatty acids, and cell proliferation were significantly suppressed by EGCG and TF-3 [7]. These findings suggest that tea polyphenols suppress FAS expression by down-regulating EGF receptor/PI3K/Akt/Sp-1 signal transduction pathways. Tea and tea polyphenols might induce hypolipidemic, antiobesity, and antiproliferative effects by suppressing FAS (Fig. 2). The molecular mechanisms of these biochemical reactions will be discussed later.

7 Stimulation of cellular energy expenditure by tea drinking in rodents

Maintenance of a constant body weight requires a balance between cellular energy intake (EI) and energy expenditure (EE) A slight imbalance in this energy equilibrium can lead to significant changes in body weight and may eventually result in obesity [25]. Functional foods that affect energy metabolism and fat partitioning may be helpful adjuncts to a dietary approach to weight control. To date, dietary fats seem to be most promising and have been the most extensively studied for their effects on body weight control. However, the weight loss observed is small and should be considered mostly as a measure to prevent weight gain. Carefully conducted clinical studies are needed to firmly ascertain the effect of tea, milk, and nuts on body weight maintenance [26]. Daily consumption of tea containing 690 mg catechins for 12 wk reduced body fat, which suggests that the ingestion of catechins might be useful in the prevention and improvement of lifestyle-related disease, mainly obesity [27].

Searching into the literatures, it is found that few studies have carefully examined the effects of tea consumption on body weight or EE. In fact, only two studies have examined the effect of tea consumption, as a beverage on EE [28, 29]. A randomized crossover design was used to compare 24-h EE of 12 men consuming each of four treatments: (a) water, (b) full-strength oolong tea (daily allotment brewed from 15 g of tea), (c) half-strength oolong tea treatment (brewed from 7.5 g tea), and (d) water containing 270 mg caffeine, equivalent to the concentration in the full-strength oolong tea treatment. Subjects refrained from consuming caffeine or flavonoids for 4 days prior to the study. Subjects received each treatment for 3 days; on the third day, EE was measured by indirect calorimetry in a room calorimeter. For the 3 days, subjects consumed a typical American diet. Energy content of the diet was tailored to each subject's needs as determined from a preliminary measure of 24-h EE by calorimetry. Relative to the water treatment, EE was significantly increased 2.9 and 3.4% for the full-strength oolong tea and caffeinated water treatments, respectively. This increase over water alone represented an additional expenditure of 281 and 331 kJ/day for subjects treated with full-strength oolong tea and caffeinated water, respectively. In addition, fat oxidation was significantly higher (12%) when subjects consumed the full-strength oolong tea rather than water [28]. It is concluded that oolong tea stimulated EE and fat oxidation in normal-weight males and would have some beneficial effects on a person's ability to maintain lower body fat.

Another recent study examined the effect of oolong tea and green tea consumption on fasting EE [29]. Eleven healthy normal-weight women were tested after drinking water and again after drinking oolong tea. Another 11 healthy normal-weight women were tested after drinking water and again drinking green tea. Resting EE was similar in the two groups before consumption of the different beverages and remained low after water and green tea consumption but increased significantly after oolong tea consumption. The

cumulative increase in EE over resting EE after the consumption of oolong tea, green tea, and water was 110.7 (26.5 kcal), 49.5 (11.8 kcal), and 11.2 kJ (2.7 kcal), respectively, over the 2-h measuring period [31]. The authors concluded that, because oolong tea had less caffeine and EGCG than did green tea, the rise in EE must be due to the presence in oolong tea of more polymerized polyphenols than are found in green tea.

Another study that examined the effects of green tea on thermogenesis in humans [10]. Green tea has thermogenic properties and promote fat oxidation beyond that explained by its caffeine content *per se*. The green tea extract may play a role in the control of body composition *via* sympathetic activation of thermogenesis, fat oxidation, or both [10]. Fundamentally, there are only two ways to treat obesity: Reduce EI or increase EE. Because thermogenesis and fat oxidation are to a large extent under the control of the sympathetic nervous system and its neurotransmitter norepinephrine that provide a rational approach for obesity management [30]. In this context, there has been attracted interest in the potential thermogenic effects of many compounds extracted from plants, namely caffeine from coffee and tea, ephedrine from ephedra, and capsaicin from pungent spices, largely because of their potential to modulate catecholamine release and activity [31].

8 General remarks on the action mechanisms involving in the hypolipidemic and antiobesity effects of tea and tea polyphenols

It seems to be a traditional Chinese belief that drinking tea promotes good health and longevity [32]. To support this belief, the scientific evidence is rapidly accumulating. Tea is one of the most frequently consumed beverages worldwide, yet very little is known about its metabolic effects in humans. Caffeine is generally regarded as the major metabolically active compound in tea. Some individuals are sensitive to caffeine and find that it induces sleeplessness or irritation to the gastrointestinal tract, but others consume it specifically because it is a mild stimulant and increases alertness and metabolic rate [28].

The effect of caffeine on metabolic rate has been well documented. Significant increase of 2–12% in metabolic rate is observed with caffeine doses of 200–300 mg [33]. It is concluded that EGCG and caffeine from the tea act synergistically to produce the thermogenic response and an increase in fat oxidation [10]. It is clear that the consumption of oolong tea stimulates both EE and fat oxidation in normal-weight man. This raises the possibility that tea consumption could have some beneficial effect on an individual's ability to maintain a lower body fat content [28].

The effects of the green tea catechin, EGCG, were dose-dependent and gender and strain independent. In addition, differential effects of green tea catechins on body weight loss, food intake restriction, decreases in accessory sexual organ weight, and decreases in blood nutrients were observed [15]. The effect of EGCG on the weight of male accessory sexual organs was due to lowered circulating levels of testosterone. Furthermore, we have demonstrated that microsomal 5α-reductase, a key enzyme to convert testosterone to its active form dihydrotestosterone, was significantly inhibited by tea polyphenols including EGCG and theaflavins [34].

The administration of green tea extract is reported to increase fat oxidation and EE in humans [10] and in rat brown adipose tissue [11], and it has been assumed to be attributable to an interaction between green tea extract's high catechins and caffeine content that influences the level of sympathetic activity. Since catechins are known to inhibit catechol-*O*-methyltransferase (the enzyme that degrades norepinephrine), and caffeine is known to inhibit the phosphodiesterase-induced degradation of cAMP, it has been proposed that these compounds synergistically prolong and augment the sympathetic stimulation of fat oxidation [11]. The molecular mechanism by which tea catechins stimulate lipid metabolism is unclear. It has become apparent that the expression of many lipid metabolizing enzymes, including acyl-CoA oxidase and acyl-CoA dehydrogenase, is transcriptionally regulated by peroxisome proliferator-activated receptors (PPARs). It has been shown that catechins (EGCG, ECG, GCG, *etc.*) are not ligands for PPARα by using a transient transfection assay [8]. On the other hand, nuclear factor-κB (NF-κB) was reported to inhibit PPARα-mediated activation of a PPAR response element-driven promoter through physical interaction of PPARα with NF-κBp65 [35]. Because catechin gallates inhibit the activation of NF-κB [36, 38], feeding with tea catechins regulates the transcription of PPAR-related genes by reducing the NF-κB activation, which may lead to up-regulation of the lipid metabolizing enzymes.

One of the intracellular signaling pathways that are frequently activated in cancer cells is the PI3K/Akt kinase pathway [37]. This pathway has been documented as an important signaling for cell survival, cell transformation, and tumor growth. PI3K catalyzes the formation of PIP2 and IP3. Increases in phosphoinositides lead to membrane translocation of downstream effectors such as the Ser/Thr protein kinase Akt. On translocation, Akt is phosphorylated and activated by phosphatidylinositol-3,4,5–triphosphate-dependent kinase (PDK), ultimately resulting in the stimulation of cell growth and survival through transcription acti-

vation of the FAS gene [7]. Our published data indicate that the activated Akt may bind on the Sp-1 site that leads to transcription of the FAS gene as illustrated in the Fig. 2. The suppression of FAS expression by tea polyphenols including EGCG, TF-1, TF-2, and TF-3 has been demonstrated [7].

FAS plays a central role in *de novo* lipogenesis in mammals by the action of its seven active sites. FAS catalyzes all the reactions in the conversion of acetyl-CoA and malonyl-CoA to palmitate. FAS concentration is sensitive to nutritional and hormonal status in lipogenic tissues such as liver and adipose tissues. The nutritional regulation of FAS occurs mainly *via* changes in FAS gene transcription [38]. Our studies also showed that the incorporation of ^{14}C-acetyl-CoA into triglyceride, fatty acid, and cholesterol in MCF-7 cells was significantly inhibited by EGCG and TF-3 [7]. These results have provided evidence that tea polyphenols such as EGCG and TF-3 profoundly suppress FAS gene transcription through EGF receptor/PI3K/Akt/Sp-1 signal transduction pathways.

In present review, we have demonstrated that cancer cell proliferation is profoundly inhibited by tea polyphenols including catechins and theaflavins by suppression of the function of EGF receptor [39–41] that lead to the blockade of MAPK/MEK/ERK/ELK signal pathway [42, 43] and PI3K-dependent pathway [44]. In the present study, we have shown that FAS expression is significantly inhibited by tea polyphenols also through suppression of the function of the EGF receptor that leads to the inhibition of PI3K/Akt/Sp-1 signal pathway [7].

9 Recent advances on the action mechanism of antiobesity effects by tea polyphenols

Tea polyphenols, especially EGCG, have been proposed as a chemopreventive for obesity, diabetes, cancer, neurodegenerative disorders, and cardiovascular diseases; however, relatively little is known about the mechanism of action of EGCG on fat cell function. Preadipocyte (3T3 L1) proliferation was inhibited by EGCG in dose-, time-, and growth phase-dependent manner [45]. EGCG decreased levels of phosphor-ERK1/2, cdk2 and cyclin D1 proteins, reduced Cdk2 activity, and increased levels of Go/G1 growth arrest, $p21^{waf/cip1}$ and $p27^{kip1}$, but not $p18^{ink}$, proteins and their associations to cdk2. Results of this study may relate to the mechanism by which EGCG modulate body weight.

Another study has shown that green tea catechins promote loss of body weight fat and inhibit growth of many cancer cell types by inducing apoptosis [46]. EGCG had not effect on either viability or apoptosis of preconfluent 3T3 L1 preadipocytes. EGCG also did not affect viability of mature adipocytes; however, EGCG increased apoptosis in mature adipocytes. Furthermore, EGCG dose-dependently inhibited lipid accumulation in maturing preadipocytes [46]. These results demonstrate that EGCG can act directly to inhibit differentiation of preadipocytes and to induce apoptosis of mature adipocytes and thus could be an important adjunct in the treatment of obesity.

For mechanism of the antiobesity actions, green tea significantly stimulated the glucose uptake accompanied by a decrease in translocation of glucose transporter 4 (GLUT 4) in adipose tissue, while it significantly stimulated the glucose uptake with GLUT 4 translocation in skeletal muscle [47]. Moreover, green tea suppressed the expression of peroxisome proliferator-activated receptor γ and the activation of sterol regulatory element binding protein-1 in adipose tissues. Therefore, green tea exert its antiobesity actions through modulating glucose uptake system in adipose tissue and skeletal muscle and suppressing the adipogenesis-related transcription factors [47].

Recently, the suppressive effects of tea catechins on the differentiation of 3T3L1 preadipocytes to adipocytes were further investigated [48]. CG, EGC, ECG, and EGCG at 5 μM suppressed intracellular lipid accumulation. These catechins inhibited the expression of PPARγ^2 and CCAAT/enhancer-binding protein (C/EBP)α, both of which act as key transcription factors at an early stage of differentiation, followed by the expression of GLUT 4 at a later stage. Thus, catechins suppressed adipocyte differentiation accompanied by the down-regulation of PPARγ^2, C/EBPα, and GLUT 4.These results suggested that tea polyphenols prevent obesity through the suppression of adipocyte differentiation [48]. The inhibition of obesity can also be achieved through down-regulating FAS expression in the nucleus and stimulating EE in the mitochondria by tea and tea polyphenols as illustrated in Fig. 2.

It is proposed that in mitochondria, tea and tea polyphenols may stimulate the cellular EE that may reduce the body weight gain [28, 29]. Meanwhile, in the nucleus, the expression of FAS may be suppressed by tea and tea polyphenols through down-regulating EGF-receptor/PI3K/Akt/Ap-1 signal transduction pathways that may lead to inhibit plasma lipids and cell growth [1, 7].

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10 References

[1] Kuo, K. L., Weng, M. S., Chiang, C. T., Tsai, Y. J. *et al.*, *J. Agric. Food Chem*. 2005, *53*, 480 – 489.

[2] Rietveld, A., Wiseman, S., *J. Nutr*. 2003, *133*, 3285s – 3292s.

[3] Crespy, V., Williamson, G., *J. Nutr*. 2004, *134*, 3431s – 3440s.
[4] Lin, Y. S., Tsai, Y. J., Tsai, J. S., Lin, J. K., *J. Agric. Food Chem*. 2003, *51*, 1864 – 1873.
[5] Ho, C. T., Chen, Q. Y., Shi, H., Zhang, K. Q., Rosen, R. T., *Prev. Med*. 1992, *21*, 520 – 525.
[6] Must, A., Spadano, J., Coakley, E. H., Field, A. E. *et al.*, *JAMA* 1999, *282*, 1523 – 1529.
[7] Yeh, C. W., Chen, W. J., Chiang, C. T., Lin-Shiau, S. Y., Lin, J. K., *Pharmacogenomics J*. 2003, *3*, 267 – 276.
[8] Murase, T., Nagasawa, A., Suzuki, J., Hase, T., Tokimitzu, I., *Int. J. Obes. Relat. Metab. Disord*. 2002, *9*, 3 – 8.
[9] Han, L. K., Takuma, T., Li, J., Kimura, Y., Okuda, H., *Int. J. Obes.* 1999, *23*, 98 – 105.
[10] Dulloo, A. G., Duret, C., Rohrer, D., Girardier, L. *et al.*, *Am. J. Clin. Nutr*. 1999, *70*, 1040 – 1045.
[11] Dulloo, A. G., Seydoux, J., Girardier, L., Chantre, P., Vandermander, J., *Int. J. Obes. Relat. Metab. Disord*. 2000, *24*, 252 – 258.
[12] Liao, S., *Hong Kong Med. J*. 2001, *7*, 369 – 374.
[13] Zheng, G., Sayama, K., Okubo, T., Juneja, L. R., Oguni, I., *In Vivo* 2004, *18*, 55 – 62.
[14] Lin, Y. L., Cheng, C. Y., Lin, Y. P., Lau, Y. W. *et al.*, *J. Agric. Food Chem*. 1998, *46*, 1893 – 1899.
[15] Kao, Y. H., Hiipakka, R. A., Liao, S., *Endocrinology* 2000, *141*, 980 – 987.
[16] Klaus, S., Pultz, S., Thone-Reineke, C., Wolfram, S., *Int. J. Obesity* 2005, *29*, 615 – 623.
[17] Mayes, P. A., Botham, K. M., in: Murray, R. K. *et al.* (Eds.), *Harper's Illustrated Biochemistry* (26th edn.), Lange Medical Books, New York 2003, pp. 173 – 179.
[18] Vison, J. A., Teufel, K., Wu, N., *J. Agric. Food Chem*. 2004, *52*, 3661 – 3665.
[19] Ikeda, I., Buda, K., Suzuki, Y., Kobayashi, M. *et al.*, *J. Nutr*. 2005, *135*, 155 – 159.
[20] Smith, S., *FASEB J*. 1994, *8*, 1245 – 1259.
[21] Kuhajda, F. P., *Nutrition* 2000, *16*, 202 – 208.
[22] Wang, X., Tian, W. X., *Biochem. Biophys. Res. Commun*. 2001, *288*, 1200 – 1206.
[23] Wang, X., Song, K. S., Guo, Q. X., Tian, W. X., *Biochem. Pharmacol*. 2003, *66*, 2039 – 2047.
[24] Kuhajda, F. P., Pizer, E. S., Li, J. N., Mani, N. S. *et al.*, *Proc. Natl. Acad. Sci. USA* 2000, *97*, 3450 – 3454.
[25] Hill, J. O., Wyatt, H. R., Reed, G. W., Peters, J. C., *Science* 2003, *299*, 853 – 855.
[26] St-Onge, M.-P., *Am. J. Clin. Nutr*. 2005, *81*, 7 – 15.
[27] Nagao, T., Komine, Y., Soga, S., Meguro, S. *et al.*, *Am. J. Clin. Nutr*. 2005, *81*, 122 – 129.
[38] Rumpler, W., Seale, J., Clevidence, B., Judd, J. *et al.*, *J. Nutr*. 2001, *131*, 2848 – 2852.
[29] Komatsu, T., Nakamori, M., Komatsu, K., Hosoda, K. *et al.*, *J. Med. Invest*. 2003, *50*, 170 – 175.
[30] Landsberg, L., Young, J. B., *Int. J. Obes. Relat. Metab. Disord*. 1993, *65*, 829 – 834.
[31] Dulloo, A. G., *Br. J. Nutr*. 1998, *80*, 493 – 494.
[32] Yang, C. S., Landau, J. M., *J. Nutr*. 2000, *130*, 2409 – 2412.
[33] Astrup, A., Taubro, S., Cannon, S., Hein, P. *et al.*, *Am. J. Clin. Nutr*. 1990, *51*, 759 – 767.
[34] Lee, H. H., Ho, C. T., Lin, J. K., *Carcinogenesis* 2004, *25*, 1101 – 1118.
[35] Delerive, P., De Bosscher, K., Besnard, S., Vanden Berghe, W., *J. Biol. Chem*. 1999, *274*, 32048 – 32054.
[36] Lin, Y. L., Lin, J. K., *Mol. Pharmacol*. 1997, *52*, 465 – 472.
[37] Blame-Jensen, P., Hunter, T., *Nature* 2001, *411*, 355 – 365.
[38] Moon, Y. S., Latasa, M., Griffin, M. J., Sul, M. S., *J. Lipid Res*. 2002, *43*, 691 – 698.
[39] Liang, Y. C., Lin-Shiau, S. Y., Chen, C. F., Lin, J. K., *J. Cell. Biochem*. 1997, *67*, 55 – 65.
[40] Liang, Y. C., Lin-Shiau, S. Y., Chen, C. F., Lin, J. K., *J. Cell. Biochem*. 1999, *75*, 1 – 12.
[41] Lin, J. K., *Arch. Pharm. Res*. 2002, *25*, 361 – 371.
[42] Lin, J. K., Liang, Y. C., Lin-Shiau, S. Y., *Biochem. Pharmacol*. 1999, *58*, 911 – 915.
[43] Chung, J. Y., Park, J. O., Phyu, H., Dong, Z. *et al.*, *FASEB J*. 2001, *15*, 2012 – 2024.
[44] Normura, M., Kaji, A., He, Z., Ma, N. Y. *et al.*, *J. Biol. Chem*. 2001, *276*, 46624 – 46631.
[45] Hung, P. F., Wu, B. T., Chen, H. C., Chen, Y. H., *et al.*, *Am. J. Physiol. Cell. Physiol*. 2005, *288*, C1094 – C1108.
[46] Lin, J., Della-Fera, M. A., Baile, C. A., *Obes. Res*. 2005, *13*, 982 – 990.
[47] Ashida, H., Furuyashiki, T., Nagayasu, H., Bessho, H. *et al.*, *Biofactors* 2004, *22*, 135 – 140.
[48] Furuyashiki, T., Nagayasu, H., Aoki, Y., Bessho, H. *et al.*, *Biosci. Biotechnol. Biochem*. 2004, *68*, 2353 – 2359.

