Abstract

AP-1

GREEN TEA CATECHINS, ENDOCRINE SYSTEMS, AND FAT CELL

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Adipocytes have been traditionally viewed as the depot site for fat energy. They are now known to express and secrete a variety of bioactive peptides that act the autocrine, paracrine, and endocrine levels. Their endocrine, mitogenic, and metabolic activities can be regulated by polyphenolic nutrients and other hormones. Accordingly, we used mice and murine preadipocytes and adipocytes to carry out a series of experiments: 1) to understand the mechanisms of how green tea epigallocatechin gallate (EGCG) acted on the mitogenesis, glucose uptake, lipid accumulation, differentiation, and resistin gene expression in fat cells, 2) to understand the mechanisms of how EGCG interacted with insulin to regulate preadipocyte mitogenesis and adipocyte glucose uptake, and 3) to understand the mechanisms of how adipocyte resistin hormone was regulated by estrogens, environmental estrogens, and IGF-I.

Green tea EGCG is a polyphenolic flavonoid (once called vitamin P) that has been found to reduce body weight and body fat, in addition to the incidence of cancers and diabetes. The antiobesity effect of EGCG is supported by our data that it reduces food uptake and serum levels of insulin and IGF-I and by other laboratory in vivo data that it inhibits lipid absorption and stimulates energy expenditure. In vitro, we discovered that EGCG inhibited preadipocyte mitogenesis and adipocyte differentiation, stimulated fat cell apoptosis and reactive oxygen species (ROS) production, suppressed insulin-stimulated preadipocyte mitogenesis and adipocyte glucose uptake, inhibited glycerol-3-phosphate dehydrogenase (G3PDH) activity, and downregulated adipocyte resistin expression. EGCG exerted its antimitogenic effect on preadipocytes via the ERK and Cdk2 pathways, reduced levels of adipogenesis-related transcriptional factors, such as C/EBPβ and PPARγ, of differentiating 3T3-L1 preadipocytes, induced preadipocyte apoptosis via the Cdk2 and caspase-3 pathways, increased ROS production in preadipocytes and adipocytes via the glutathione (GSH) and 67-kDa laminin receptor (67LR; an EGCG receptor) pathways, suppressed insulin stimulation of preadipocyte mitogenesis via the anti-insulin receptor signaling and 67LR pathways, reduced insulin-stimulated glucose
uptake in adipocytes via the 67LR and AMP-activated protein kinase pathways, inhibited G3PDH activity with a Ki of 18 μM in a non-competitive manner, and inhibited adipocyte resistin gene expression via the ERK pathway. EGCG was more effective than other green tea catechins in affecting fat cell activity. The signal of EGCG in reducing growth of 3T3-L1 preadipocytes differed from that of 3T3 fibroblasts. Other laboratory in vitro studies indicated that EGCG stimulated thermogenesis and inhibited the activities of pancreatic lipase, acetyl-CoA carboxylase, and fatty acid synthase. Whether EGCG has the health benefits on human obesity in clinical studies is discussed.

In addition, we discovered that adipocyte resistin hormone was regulated by 17β-estradiol, environmental estrogens, and insulin-like growth factors I. 17β-Estradiol upregulated adipocyte resistin gene expression via the estrogen receptor, ERK, and C/EBPα pathways. Environmental estrogens, such as octylphenol, stimulated resistin gene expression in 3T3-L1 adipocytes via the estrogen receptor and ERK pathways. In vivo, octylphenol reduced adiponectin levels and increased resistin and glucose levels. IGF-I downregulated resistin gene expression in 3T3-L1 adipocytes via IGF-I receptor-dependent and MEK1-, p38 MAPK-, and PI3K-independent pathways and modified the distribution of resistin between the intracellular and extracellular compartments via a p38 MAPK- dependent pathway.