Food Components with Anti-Obesity Effect

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Abstract

Although many food components are reportedly beneficial to body-weight management, lack of understanding of molecular mechanisms and their function in overall adiposity under physiological conditions hinders successful and safe development of antiobesity functional foods. A positive energy balance resulting from an increase in food intake, a reduced energy expenditure, and/or dysfunction of adipose biology is associated with the development of obesity. This article provides an overview of the components involved in energy balance and adipose development and function. There is evidence that numerous ingredients found in foods can modulate energy balance and adipose biology, thereby potentially lowering adiposity.

INTRODUCTION

BMI: body-mass index

Obesity confers an adverse effect on health and is recognized as a leading global health concern. It is a disease associated with accumulation of an excess amount of body fat. Body fat can be easily measured by a formula called body-mass index (BMI), which combines weight and height with an assumption of a cylindrical shape of the whole body with uniform density. According to guidelines from the World Health Organization (WHO), overweight in adults is defined as a BMI of 25.0 to 29.9, and obesity is defined as a BMI of 30.0 or higher (World Health Report 2002). Obesity in adults has dramatically increased in every continent. The National Health and Nutrition Examination Survey (NHANES) has shown a striking increase in the prevalence of obesity over time in the United States. The most recent data from the NHANES (2007–2008) show that approximately 32.2% of U.S. men and approximately 35.5% of U.S. women are obese (Ogden et al. 2010). Of these, African-American adults had the highest rates of obesity, followed by Mexican-Americans and Caucasians. In Europe, a recent epidemiological study revealed that the prevalence of obesity ranged from 4.0% to 28.3% and 6.2% to 36.5% in men and women, respectively, depending on geographic location, with higher prevalence in Central, Eastern, and Southern Europe (Berghofer et al. 2008). A dramatic increase in overweight and obesity prevalence was also observed in mainland China. In 2002, the prevalence of overweight and obesity in Chinese adults was 22.8% and 7.1%, respectively, which was an increase of 40.7% and 97.2%, respectively, over 1992 (Chen 2008).

The increasing prevalence of obesity is not confined only to adults. The most recent data from the NHANES show that childhood obesity in the United States has tripled since 1980. However, it seems to have remained steady with no decrease during the past 10 years. In 2007–2008, almost 12% of children in the United States were reported to be obese (Ogden et al. 2010). In Europe, in 2006, 31.8% of school-aged children were either overweight or obese, with 7.9% of children being obese (Fussenegger et al. 2008). Similarly, more than 29% of boys and 17% of girls in China were reported to be overweight or obese in 2000 (Chen 2008). A rapidly increasing population of overweight children has been observed in many countries, and the overweight children are likely to remain obese in their adulthood.

Obesity is associated with an increased risk of chronic diseases such as type 2 diabetes and coronary heart disease (Semenkovich 2006, Weyer et al. 2000), suggesting the importance of body fat as a contributor to these diseases. Previous studies demonstrated that specific nutrients in diets and foods might play an important role in body-weight management and controlling obesity-associated diabetes (Ludwig et al. 1999, Tuomilehto et al. 2001). These studies suggest that some bioactive food components are effective for prevention of obesity and its related health complications.

This review provides an overview of the biological function of the components involved in energy balance, as well as adipose development and function. This review also investigates evidence of the effect of bioactive food components and their mode of action in regulating body fat gain and obesity, and focuses on directions for future work toward dietary prevention of obesity.

ENERGY BALANCE AND OBESITY

Obesity is influenced by an interaction between genetic, environmental, and psychosocial factors, which together contribute to alteration of the energy balance equation (the balance between energy intake and expenditure) (Kopelman 2000). Although genetic factors certainly play an important role in determining genetic susceptibility to obesity within a population, the dramatic increase in the prevalence of obesity in recent years suggests the involvement of nongenetic factors, such as

environmental and psychosocial factors, in changes in energy balance. Examples of these include an increase in energy density in diet by having refined foods with more simple sugars and less fiber, and/or increased fat content due to urbanization and economic development. This is usually accompanied by an altered eating behavior that includes consuming more processed foods and beverages, and consuming less whole grains, fruits, and vegetables (Gardner & Rhodes 2009).

The energy balance equation represents a balanced conversion of food and oxygen to carbon dioxide, water, heat, and work in the body. Obesity develops when energy intake, in the form of feeding, exceeds energy expenditure, which consists of physical activity, basal metabolism, and adaptive thermogenesis. The result is storage of excess energy in adipose tissue. Accordingly, prevention of obesity could be achieved through modulating energy balance by lowering energy intake or increasing energy expenditure. Moreover, inhibition of accumulation of excess energy storage in adipose tissue could also attribute to reducing the incidence of obesity. However, our understanding of the regulation of energy balance and adipose function by bioactive food components is poor. Thus, this review first focuses on the critical details about the molecular and biochemical basis of food intake, energy expenditure, and adipose function in obesity. The effects of some dietary components on energy balance and adipose function are discussed later in the review.

CNS: central nervous system

CCK: cholecystokinin

GLP-1: glucagon-like peptide-1

PYY: peptide YY

Regulation of Energy Intake by Peptides and Hormones

The regulation of energy intake through an appetite-mediated central network in the hypothalamus has been extensively reviewed (Schwartz et al. 2000, Woods & D'Alessio 2008). Briefly, signaling peptides produced from peripheral tissues such as adipose tissue, pancreas, and gut are known to link peripheral adiposity and energy homeostasis to central nervous system (CNS)-regulated food intake. The following are important signaling molecules affecting central control of energy intake and energy balance: leptin secreted from adipocytes; insulin secreted from the pancreas; and cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and ghrelin secreted from the gastrointestinal tract (**Table 1**).

Leptin was the first hormone discovered that links energy storage in adipocytes to negative feedback regulation of food intake in brain, specifically the hypothalamus (Zhang et al. 1994). Given that leptin is largely produced from adipose tissue, its plasma level is proportional to total body fat content (Considine et al. 1996, Schwartz et al. 1996). The interaction between leptin and the hypothalamic leptin receptor is reported to facilitate leptin uptake and its food intake

Table 1 Peptides/hormones implicated in the regulation of energy balance

Molecule	Produced by	Function(s) in energy balance
CCK	Intestine (mucosa)	Lowering food intake
GLP-1	Pancreas, intestine, brainstem	Lowering food intake, appetite and body weight gain
PYY	Intestine	Lowering food intake
Ghrelin	Stomach	Stimulating appetite and food intake
Leptin	Adipose tissue	Lowering food intake
Insulin	Pancreatic β-cells	Lowering food intake and stimulating energy expenditure
NPY	Brain (hypothalamus)	Stimulating food intake and lowering energy expenditure
α-MSH	Pituitary gland	Lowering food intake
AgRP	Brain (hypothalamus)	Stimulating food intake and lowering energy expenditure
Adiponectin	Adipose tissue	Stimulating food intake and lowering energy expenditure (during fasting)

AgRP: agouti-related peptide

NPY: neuropeptide Y

POMC: prepropeptide proopiomelanocortin

regulation in the brain (Tartaglia et al. 1995). This is through leptin-induced cleavage of prepropeptide proopiomelanocortin (POMC) to form α-melanocyte-stimulating hormone (α-MSH), whose binding to melanocortin receptors is known to trigger the catabolic pathway and a decrease in food intake (Schwartz et al. 2000). Conversely, a reduced level of circulating leptin contributes to increasing hyperphagia and body fat by leptin deficiency–activated hypothalamic agouti-related peptide (AgRP)- and neuropeptide Y (NPY)-dependent anabolic pathways. Simultaneously, the leptin deficiency–induced release of AgRP protein in the hypothalamus suppresses the inhibitory function of POMC in food intake.

The body adiposity is sensed by the pancreatic hormone insulin. The generation and secretion of insulin from pancreatic β-cells are proportional to body fat content and whole body insulin sensitivity (Bagdade et al. 1967). Insulin entering the CNS is also involved in regulating food intake and energy homeostasis through its binding to the insulin receptor located in ARC neurons in the hypothalamus (Benoit et al. 2002, Grossman 1986). Similar to leptin, the catabolic and anabolic action of insulin in the hypothalamus relies upon insulin receptor–mediated activation of POMC neurons and NPY/AgRP neurons, respectively.

It should be noted that although both adiposity hormones leptin and insulin are involved in the central control of energy homeostasis, elevated levels of leptin and its receptor in the brain are likely required for effective regulation of central food intake and energy balance. Accordingly, both the administration of leptin or leptin receptor agonists and the activation of the leptin-sensing POMC pathway in the hypothalamus have been suggested to be useful therapeutic strategies for reduced food intake and obesity prevention. However, because of potential side effects (e.g., psychiatric concerns), few pharmacological treatments are successful in long-term use for body-weight management through central regulation of food intake (Bray 2009). Furthermore, central control of food intake by dietary bioactive components is associated with a number of limitations. These include poor stability and bioavailability during digestion and absorption, and poor blood-brain barrier–penetrating abilities.

The gut is an endocrine organ that synthesizes and releases many peptides that regulate various components, such as the size and the frequency of meals, of energy balance. Therefore, the gut peptides contribute to changes in body weight and ingestive behavior by transmitting endocrine and neural signals to the hypothalamus and brainstem to influence food intake, mainly short-term feelings of hunger and satiety. Among more than 20 well-documented gut hormones that control appetite are CCK, GLP-1, PYY, and ghrelin.

CCK is a satiety hormone released postprandially from the small intestine to inhibit food intake through its binding to the G protein–coupled CCK receptors in the hindbrain, which in turn transfers signals to the hypothalamus for appetite control (Moran 2000, Smith & Gibbs 1975). Beside its effect of lowering food intake, CCK also delays gastric emptying, stimulates secretion of pancreatic digestive enzymes, and contracts the gall bladder in response to nutrients in the gut. Thus, regulation of food intake by CCK and its binding to the CCK receptors might be an attractive idea. However, apparently it is likely to be effective only in short-term control of appetite because a study of continuous infusion of CCK showed little effect on food intake in animals (Crawley & Beinfeld 1983).

GLP-1 is a gene product of preproglucagon that is highly expressed in the pancreas, intestine, and brainstem. A series of proteolytic cleavages is known to facilitate the release of the active form of GLP-1 and other satiety-controlling peptides such as GLP-2 and oxyntomodulin from the preproglucagon (Holst 2004). Secretion of GLP-1 is sensed by nutrient presence, causing both short-term control of appetite and long-term control of body-weight gain through binding to its specific receptor in the pancreas (Drucker 2006). Animal and human studies suggest a potential role of GLP-1 in lowering food intake, appetite, and weight gain (Drucker 2006, Turton et al.

1996). Moreover, a negative correlation between circulating GLP-1 level and adiposity has been observed (Verdich et al. 2001).

PYY is another satiety gut hormone from the same peptide family as NPY (Larhammar 1996). There are two forms of PPY, PPY_{1-36} and PPY_{3-36}, with the latter being the major form found in circulation (Eberlein et al. 1989). PPY secreted by the gut has been shown to influence gastrointestinal responses similar to CCK. Particularly, low-dose intravenous infusion of PYY is shown to reduce food intake in animals and humans (Batterham et al. 2002, Chelikani et al. 2006).

Ghrelin is a hormone released from the stomach, and its secretion is increased by fasting. It is known to stimulate appetite (Asakawa et al. 2001, Kojima et al. 1999). Acylation of secreted ghrelin plays a critical role in facilitating its binding to the growth-hormone-secretagogue receptor (GHS-R) in the brain (Kojima et al. 1999). Conversely, impairment of ghrelin gene expression results in reduced food intake and incidence of obesity in animals (Wortley et al. 2005). This hunger hormone might be a useful target for treating obesity because administration and central infusion of ghrelin promote adiposity in experimental animals (Theander-Carrillo et al. 2006, Tschop et al. 2000).

Taken together, any changes in the expression and function of these gut hormones, and in their binding abilities to their specific receptors in CNS, should be considered in developing dietary strategy for the control of appetite. Recent studies have provided evidence that consumption of coffee (Tunnicliffe & Shearer 2008), some isoflavones (Zhang et al. 2009), and fatty acids with various chain length (Poppitt et al. 2010) has a beneficial function in lowering satiety potentially through suppression of satiety hormone release.

BMR: basal metabolic rate

UCPs: uncoupling proteins

BAT: brown adipose tissue

Regulation of Energy Expenditure by Uncoupling Proteins

Excess energy entering the body as food should be expended as work or heat in order to maintain energy balance. Basal metabolic rate (BMR), physical exercise, and adaptive thermogenesis are known to contribute to energy expenditure. However, adaptive thermogenesis (i.e., facultative thermogenesis) is important in regulating energy expenditure in response to environmental temperature and food intake. Adaptive thermogenesis activated by cold and diet is believed to be responsible in the mitochondria for combusting stored or excess energy into heat as measured calories. One mechanism underlying mitochondrion-mediated thermogenesis is uncoupling of calorie burning and adenosine triphosphate (ATP) synthesis, resulting in loss of energy as heat. This is through a leakage of protons to the mitochondrial membrane, thereby bypassing ATP synthesis and activation of various mitochondrial inner membrane–bound uncoupling proteins (UCPs) UCP-1 to UCP-5 (Adams et al. 2001). These UCPs are members of the mitochondrial anion carrier superfamily. Although UCP-2 is expressed in various tissues, UCP-1 is expressed mainly in brown adipose tissue (BAT), which is a dark-colored, mitochondrion-rich adipose tissue with an enhanced ability for respiratory uncoupling and adaptive thermogenesis. UCP-3 is highly expressed in BAT and muscle, and UCP-4 and UCP-5 are largely expressed in the CNS (Adams et al. 2001). The role of UCPs in energy expenditure and thermoregulation is known from many studies. For example, mice overexpressing UCP-1 (Li et al. 2000) or UCP-3 (Clapham et al. 2000, Tiraby et al. 2007) were resistant to diet-induced obesity and showed improved insulin sensitivity. Although UCP-1, UCP-2, and UCP-3 knockout mice were not obese, these mice were sensitive to cold and had impaired thermogenesis and/or elevated levels of reactive oxygen species (ROS) (Arsenijevic et al. 2000, Gong et al. 2000). The amount of β-adrenergic receptor-dependent sympathetic nervous system–induced cyclic AMP and elevated levels of free fatty acids in BAT are known to mediate UCP-1-induced thermogenesis. It should be noted that UCP-regulated thermogenesis is also tightly linked to various energy metabolisms such as fatty acid oxidation,

mitochondrial biogenesis, and glucose homeostasis (Kozak & Anunciado-Koza 2008, Lowell & Spiegelman 2000). Thus, these studies suggest that physiological activation of UCPs might be beneficial to achieving positive energy expenditure, thereby treating obesity and its related energy disorders.

AMPK: AMP-activated protein kinase

Role of Adipose Tissue in Obesity

Traditionally adipose tissue has been viewed as an energy storage organ. During the past decade, adipose tissue has been recognized as an endocrine tissue. Adipose tissue integrates various homeostatic processes, such as energy balance, through synthesis and secretion of adipose-specific peptide hormones such as leptin, adiponectin, and resistin. Besides its role in the central control of food intake, leptin secreted from adipose tissue also contributes to improving energy homeostasis in peripheral tissues such as the liver and muscle. This occurs by lowering intracellular lipids and improving insulin sensitivity through activation of AMP-activated protein kinase (AMPK)-dependent signaling pathways (Minokoshi et al. 2002). Adipose tissue secreted factor adiponectin, also referred to as ACRP30, adipoQ, and apM1 (**Table 1**) (Yamauchi et al. 2001), regulates both glucose and lipid metabolism. Adiponectin is known to target AMPK activity to decrease gluconeogenesis and increase glucose uptake and fatty acid oxidation in the liver and muscle, resulting in ameliorating insulin sensitivity (Yamauchi et al. 2002). Unlike other adipocyte-secreted peptides, the inverse correlation between circulating adiponectin level and adiposity suggests a possible strategy of stimulating adiponectin secretion in obese and/or diabetic patients. In the CNS, adiponectin and its receptors have been shown to stimulate food intake and decrease energy expenditure through activation of AMPK (Kubota et al. 2007). In addition to leptin and adiponectin, resistin, also referred to as FIZZ3 and adipose-specific secretory factor (ADSF) (Holcomb et al. 2000, Kim et al. 2001, Steppan et al. 2001), is an adipocyte-specific hormone regulated by hormonal and nutritional signals. An elevated level of resistin is associated with adiposity and type 2 diabetes. Although more studies are needed to understand the physiological function of resistin in human obesity, it is suggested that resistin has potential proinflammatory, antiadipogenic, and prodiabetic properties (Kim et al. 2001, Reilly et al. 2005, Steppan et al. 2001). Interestingly, a recent study implicates resistin in hypothalamic control of food intake through inhibiting the hyperphagic effect of NPY (Brown et al. 2009).

Adipose tissue grows by hypertrophy (cell size increase) and hyperplasia (cell number increase). When energy intake exceeds energy expenditure, energy continues to be stored in adipose tissue leading to hypertrophy and weight gain. Adipocyte hypertrophy in turn is known to affect the ability of adipocytes to secrete aforementioned adipose-specific hormones, proinflammatory cytokines, and free fatty acids. These secreted molecules contribute to various physiological processes such as appetite, energy expenditure, and immunity.

Although adipocyte hyperplasia is not necessary to directly promote adiposity, the adipocyte number set during childhood and adolescence is likely to have a dominant role in determining the lipid-storing capacity of adipose tissue and fat mass in adults (Spalding et al. 2008). To increase adipocyte number, mesodermal pluripotent stem cells must commit to the adipocyte lineage before differentiation. These preadipocytes are then subjected to a cellular differentiation process called adipogenesis under appropriate hormonal and nutritional signals. Adipogenesis consists of four major events: (*a*) cell confluence and growth arrest, (*b*) mitotic clonal expansion, (*c*) early transcriptional changes, and (*d*) terminal differentiation (Gregoire et al. 1998). Although it is beyond the scope of this review to discuss the details in each of these events, it should be noted that coordinated regulation of mitotic clonal expansion and early transcriptional changes are critical in determining the effectiveness of adipogenesis. Levels of cell-cycle regulators and cell

proliferation–related proteins, and their phosphorylational modification, are known to contribute to cell proliferation, DNA replication, and cell division events that occur during the mitotic clonal expansion phase. Other factors such as insulin, growth hormone, growth factors [e.g., insulin-like growth factor-I (IGF-I), transforming growth factors (TGFs), and epidermal growth factor-I (EGF-I)], glucocorticoids, intracellular cyclic AMP, and related cellular signaling pathways are known to positively or negatively regulate the mitotic clonal expansion phase (Tang et al. 2003). Once mitotic clonal expansion is activated, it triggers a subsequent transcriptional activation of adipogenic transcription factors such as the CCAAT-enhancer-binding proteins (C/EBPs) family and peroxisome proliferator-activator receptor γ (PPARγ), which orchestrates transactivation of adipocyte genes involved in cell morphological change, lipid metabolism, and synthesis of adipocyte-specific peptides and cytokines during terminal differentiation. C/EBPβ and, to a lesser extent, C/EBPδ are known to be acutely expressed upon initiation of adipogenesis, which is required for subsequent expression of PPARγ and C/EBPα in differentiating adipocytes (Rosen & MacDougald 2006). Thus, C/EBPβ is considered to be the key transcription factor that initiates the transcriptional cascade of adipogenesis through stimulation of C/EBPα and PPARγ function during the terminal stage of adipogenesis.

C/EBPs: CCAAT-enhancer-binding proteins

PPARγ: peroxisome proliferator-activator receptor γ

It is believed that modulation of cellular and molecular events in adipogenesis could serve as an effective means to control body-weight gain and obesity. However, it should be recognized that inhibiting only adipogenesis without affecting whole body energy balance could possibly contribute to adipocyte hypertrophy and/or redistribution of body fat into nonadipose peripheral tissues in physiological conditions. This would be detrimental to control of obesity and its related diseases. Therefore, other approaches to increase energy expenditure in adipocytes, such as stimulation of thermogenesis and fatty acid oxidation together with blockage of adipogenesis, should be considered to control energy balance by modulating adipose biology.

REGULATION OF OBESITY BY FOOD COMPONENTS

A number of bioactive food components have been proposed to control energy balance, thereby improving body-weight loss. Here, we summarize recent findings on some of the potential antiobesity food components and their impact on the components in energy balance and adipose biology.

Components in Fruits and Vegetables

The health benefits of fruit and vegetable consumption are well recognized and include weight control. In addition to the fiber content of fruits and vegetables, other components are known to contribute to weight management, such as components from berries, soybeans, teas, spices, and citrus.

Fiber. According to the American Association of Cereal Chemists (AACC) International, dietary fiber is defined as "the edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine." Dietary fiber includes polysaccharides, oligosaccharides, lignin, and associated plant substances. Dietary fiber promotes beneficial physiological effects including laxation and/or blood cholesterol attenuation and/or blood glucose attenuation. Dietary fiber can be divided into soluble and insoluble fiber based on water solubility. Soluble fiber is known to be a good substrate for colonic fermentation. Soluble fiber has beneficial effects on glucose and lipid metabolism due to increased viscosity of gut contents. Insoluble fiber has a relatively low fermentability, but it

also provides health benefit by its bulking capacity (Anderson et al. 2009, Papathanasopoulos & Camilleri 2010).

In addition to its well-known health benefits for cardiovascular diseases and diabetes, dietary fiber has been linked to lowering body-weight gain and reducing obesity. Suggested mechanisms of dietary fiber on prevention of obesity are increasing satiety, decreasing energy intake, and increasing fecal energy loss (Anderson et al. 2009, Astrup et al. 2010, Papathanasopoulos & Camilleri 2010, Sartorelli et al. 2008). Increased satiety of dietary fiber may come from the physical properties of dietary fiber that function to add bulk, form gels, delay gastric emptying, and reduce postprandial insulin responses (Astrup et al. 2010, Papathanasopoulos & Camilleri 2010, Salas-Salvado et al. 2008). High dietary fiber–containing meals also contribute to reduced total energy intake by lowering energy density of foods (Papathanasopoulos & Camilleri 2010). Lastly, it has been suggested that dietary fiber increases fecal energy and fat excretion (Astrup et al. 2010). There are no safety concerns associated with dietary fiber consumption. Knowledge about the influences of dietary fiber on hormonal modulation associated with food intake is seemingly inconsistent (Astrup et al. 2010, Papathanasopoulos & Camilleri 2010).

Blueberries and other berries. Consumption of berry fruits, such as blueberry, blackberry, raspberry, cranberry, and strawberry, has been associated with a number of positive impacts on human health. They are rich in antioxidants, such as anthocyanines, which are water-soluble pigments (Prior et al. 2008). Berries provide a good source of dietary fiber. Berry consumption, in particular, has been linked to reduced weight gain and appetite that are not associated with berry fiber content. Molan et al. (2008) reported that the consumption of water-soluble blueberry extracts reduced appetite in an animal model. This was not correlated with their antioxidant contents. Similar results of reduced weight gain were reported with blueberry juice in an obese animal model (Vuong et al. 2009). However, others reported no difference in body weight or body fat with whole blueberries (DeFuria et al. 2009). Purified anthocyanines from blueberries may contribute to reduced obesity in animal models (Prior et al. 2008, 2009). More studies with human trials are needed to draw any conclusions regarding consumption of berries and controlling obesity.

Soybeans. Soybeans (*Glycine max*) have been consumed for centuries in Asian countries, and serve as a good source of polyunsaturated fatty acids and protein. It is well recognized that soy consumption is associated with reduced risk of cardiovascular diseases and diabetes, prevention of certain types of cancer, and improved bone health (Cederroth & Nef 2009, Xiao 2008). Most of the health benefits of soybean consumption are linked particularly to soy protein and soy isoflavones, mainly diadzein and genistein, which are referred to as phytoestrogens because of their similarity to estrogen (Cederroth & Nef 2009, Xiao 2008). Diadzein and genistein in soy are present as glycosides, which are inactive. However, once ingested, these glycosides are hydrolyzed by intestinal bacteria, resulting in active aglycones. Diadzein can be metabolized to equol and *O*-demethyangolensin, and genistein metabolized to *p*-ethyl phenol and these metabolites are the major isoflavones observed from in vivo samples (Cederroth & Nef 2009).

There are reports linking soy consumption to reduced obesity. Suggested mechanisms involve increased energy expenditure and physical activity, and increased fatty acid oxidation (Aoyama et al. 2000, Cederroth & Nef 2009). These are supported by increased levels of AMPK and acetyl-CoA carboxylase (ACC), increased lipolysis through inhibition of cAMP phosphodiesterases by genestein, and activated PPARs. Other reports showed an inhibitory role of soy components in PPARγ and C/EBPα expression in 3T3-L1 adipocytes (Cederroth & Nef 2009, Orgaard & Jensen 2008). However, unlike a large number of studies that report health benefits of soy products on

markers of cardiovascular diseases, there are relatively limited and inconsistent reports of soy protein or isoflavone effects on obesity prevention (Bhathena & Velasquez 2002, Cederroth & Nef 2009, Orgaard & Jensen 2008). It is also not conclusive whether any effects of soy products on obesity are due to soy protein or soy isoflavones (Bhathena & Velasquez 2002, Orgaard & Jensen 2008).

Use of soy or purified soy isoflavones may pose certain health concerns, such as stimulation and/or interference with tamoxifen used as breast cancer treatment and immune-related responses (Cederroth & Nef 2009, Orgaard & Jensen 2008).

EGCG: epigallocatechin gallate

Teas. Tea is made from the leaves of the *Camellia sinensis* L. plant of the Theaceae family (Hursel & Westerterp-Plantenga 2010). There are four main types of teas, green, oolong, black, and white, depending on the maturity of the leaves and the oxidative status. Although there are differences in active components and their effects, all tea types have been linked to well-known bioactive compounds (Hursel & Westerterp-Plantenga 2010, Westerterp-Plantenga et al. 2006). Most of the health benefits of tea have been investigated using green tea, thus this review focuses on green tea.

Most short-term human studies with consumption of green tea extract and caffeine have resulted in increased energy expenditure and fat oxidation. However, two studies reported either no difference or an insignificant increase in energy expenditure and fat oxidation (Hursel & Westerterp-Plantenga 2010). In contrast, a significant reduction in body weight and body fat was found in almost all human studies in which catechins were consumed for three months or more (Diepvens et al. 2007, Hursel & Westerterp-Plantenga 2010, Westerterp-Plantenga et al. 2006).

Tea has shown to increase energy expenditure, in part through a thermogenic effect and fat oxidation, and decrease body fat and body weight (Hursel & Westerterp-Plantenga 2010). Studies also have shown that green tea limits weight regain after weight loss. The suggested mechanism is by preventing reduced energy expenditure that usually occurs with a low-energy diet (Diepvens et al. 2007). Habitual caffeine consumption may influence the effects of tea in weight maintenance after weight loss. Subjects with a low habitual caffeine intake may have better outcome than those with a high caffeine intake (Hursel et al. 2009, Westerterp-Plantenga et al. 2006).

Tea exhibits a thermogenic effect due to its catechins, which include epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate (EGCG), as well as caffeine (Westerterp-Plantenga et al. 2006). The thermogenic effect of green tea cannot be attributed solely to its caffeine content; there was a significant increase in energy expenditure and fat oxidation following consumption of green tea extract compared to placebo or to caffeine alone (Westerterp-Plantenga et al. 2006). Animal studies have shown that EGCG particularly is linked to reduced food intake and increased energy expenditure (Diepvens et al. 2007).

Suggested biochemical mechanisms for catechins and caffeine are well reviewed by Hursel & Westerterp-Plantenga (2010). Catechins stimulate nuclear factor-κB (NF-κB), which subsequently upregulates enzymes for fat oxidation. Catechins also increase norepinephrine and adenyl cyclase through the inhibition of catechol *O*-methyltransferase, resulting in increased lipolysis and decreased glucose uptake. Along with the upregulation of adenyl cyclase, caffeine increases cAMP by inhibiting phosphodiesterase, resulting in increased energy expenditure and fat oxidation via protein kinase A (Hursel & Westerterp-Plantenga 2010).

Green tea has been widely consumed in China and Japan for centuries and is regarded as safe. The major health concern over tea consumption is related to its caffeine content. One study reported a small, short-term increase in blood pressure as a result of green tea consumption, but the significance of this study needs validation because others found no effect on blood pressure or heart rate associated with tea consumption (Diepvens et al. 2007).

Capsaicin. One spice principle shown to be an effective weight management agent is capsaicin, which is the pungent component from red pepper (*Capsicum annuum*). Its analog, capsiate, from the nonpungent cultivar CH-19 Sweet (*Capsicum annuum* L.), has also been shown to be a good alternative to capsaicin because of its mild taste yet similar effects (Belza et al. 2007, Belza & Jessen 2005, Reinbach et al. 2009).

Consumption of capsaicin or capsiate is reportedly associated with reduced body weight and body fat (Kawabata et al. 2006, Kawada et al. 1986). Other reports show no effects on weight or fat mass (Lejeune et al. 2003, Snitker et al. 2009). Consumption of capsaicin has been associated with decreased energy intake only following consumption of capsaicin in food form but not capsules, indicating that sensory perception of capsaicin is significant (Westerterp-Plantenga et al. 2005, Yoshioka et al. 2004). It also has been shown that capsaicin taken with breakfast significantly reduced the desire to eat (and hunger for) lunch and mid-afternoon snack (Yoshioka et al. 1999). In contrast, others found no difference in satiety following capsaicin consumption. This may have been due to the fact that only a single exposure was tested in these reports (Smeets & Westerterp-Plantenga 2009).

The suggested mechanisms of capsaicin (or red pepper) are increased energy expenditure by way of stimulating thermogenesis and increased fat oxidation (Lejeune et al. 2003, Snitker et al. 2009, Yoshioka et al. 1999). Capsaicin has been found to stimulate adrenal medullary catecholamine secretion in rats via transient receptor potential vanilloid 1 (TRPV1) (Hursel & Westerterp-Plantenga 2010, Kawabata et al. 2009). Treatment with capsiate increased levels of UCP-1 and UCP-2 (Masuda et al. 2003), which may be the result of catecholamine's binding to β-adrenoceptors to increase thermogenesis (Hursel & Westerterp-Plantenga 2010). However, a single administration or a short-term study did not result in any significant changes in energy expenditure (Galgani et al. 2010, Smeets & Westerterp-Plantenga 2009).

Numerous human studies have shown that capsaicin is safe for human consumption (Hursel & Westerterp-Plantenga 2010, Snitker et al. 2009, Westerterp-Plantenga et al. 2005), with only a few mild and diverse gastrointestinal events reported (Snitker et al. 2009). One study has shown irreversible damage to chemosensitive primary sensory neurons in newborn rats, but damage was reversible in adult rats (Jancso et al. 1977).

Other spices. Turmeric (*Curcuma longa* L.) is a well-known food ingredient also used to treat inflammation (Maheshwari et al. 2006). Curcumin is the main bioactive polyphenol component from turmeric. Many studies have shown that curcumin lowers serum triglyceride and cholesterol levels (Srinivasan et al. 2004), but few studies have investigated its direct antiobesity effects. In mice, a high fat diet supplemented with curcumin did not affect food intake but reduced body-weight gain, adiposity, and microvessel density in adipose tissue (Ejaz et al. 2009). Others reported that curcuminoids, commercial grade curcumin [i.e., a mixture of curcumin (73.4%), demethoxycurcumin (16.1%), and bisdemethoxycurcumin (10.5%)] prevented high fat diet–induced lipid accumulation in the epididymal adipose tissue and the liver of rats (Asai & Miyazawa 2001). In both cell culture and in mice models, curcumin increased 5′AMPK phosphorylation, reduced glycerol-3-phosphate acyl transferase-1, and increased carnitine palmitoyltransferase-1 expression, leading to increased oxidation and decreased fatty acid esterification (Ejaz et al. 2009). Curcumin is also reported to decrease adipogenesis via decreasing expressions of PPARγ and C/EBPα, and/or via inhibiting mitogen-activated protein kinase (MAPK) [extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinase (JNK), and p38] phosphorylation in 3T3-L1 adipocytes (Ahn et al. 2010, Ejaz et al. 2009). Curcumin also has been shown to increase apoptosis in 3T3-L1 adipocytes (Ejaz et al. 2009).

Black pepper is from unripe berries of *Piper nigrum* Linn. The main pungent component in black paper is peperine, which is an alkaloid similar to capsaicin (Astrup et al. 2010, Srinivasan 2007). The effects of black pepper or piperine on thermogenesis are believed to be mediated by the sympathetic nervous system. However, it is not conclusive that black pepper or piperine has an effect on energy balance or thermogenesis (Astrup et al. 2010).

CLA: conjugated linoleic acid

Ginger is the rhizome from *Zingiber officinale* Roscoe. The pungent components of ginger are gingerols, shogaols, and zingerone. Ginerols are present in fresh ginger, and the other two are derived from gingerols during dehydration and degradation (Astrup et al. 2010). Similar to piperine and capsaicin, these bioactive components from ginger are known to induce sympathetic nervous system–mediated thermogenesis (Astrup et al. 2010). Others reported influence of ginger on appetite; however, the evidence is still very preliminary (Astrup et al. 2010).

Mustard comes from the seeds of different species of mustard plants, including *Sinapis alba*, *Brassica juncea*, and *Brassica nigra*. The pungent component in mustard is allyl isothiocyanate, which increases thermogenesis similar to capsaicin (Astrup et al. 2010). However, there are limited data available on the significance of mustard or allyl isothiocyanate on obesity.

Citrus extract. The interest in citrus regarding obesity is focused on *Citrus aurantium*, commonly named bitter orange, sour orange, or Seville orange (Haaz et al. 2006). The fruit is sometimes used as a food but the plant is more widely used as a dietary supplement for weight loss. The popularity for use of bitter orange is due to the ban on ephedra-containing products for weight loss. *C. aurantium* contains a compound that is similar to ephedra, called synephrine (Haaz et al. 2006). Synerphine is a sympathomimetic drug, which is primarily an α-adrenergic agonist, but also has some β-adrenergic agonist properties (Bent et al. 2004, Haaz et al. 2006).

Some limited human studies have suggested that consumption of bitter orange extract reduced body weight or body fat, and others reported no effects (Bent et al. 2004, Haaz et al. 2006). This is likely to be associated with enhancement of metabolism, suppression of appetite via reducing gut motility, and promotion of lipolysis in adipocytes (Haaz et al. 2006, Hess & Sullivan 2005). In addition, a polyphenolic mixture extract prepared from red orange, grapefruit, guarana, and bitter orange has been shown to reduce body fat. This is mediated through increasing lipolysis from adipocytes, which is stimulated by β-adrenergic agonists resulting in inhibition of cAMP-dependent phosphodiesterase (Dallas et al. 2008).

There are major health concerns over consumption of *C. aurantium*. Synerpherine is known to cause vasoconstriction, resulting in increased blood pressure and increased heart rate. *N*-methyltyramine increases blood pressure by increasing norephinephrine release, thus resulting in additive hypertensive effects. The other components from bitter orange, furocoumarins, can inhibit CYP3A4 isoenzyme, resulting in potential drug interactions, such as antifungals, glucocorticoids, or calcium-channel blockers (Bent et al. 2004, Haaz et al. 2006, Hess & Sullivan 2005). Thus, the use of bitter orange, particularly long-term, needs close evaluation.

Lipid-Based Components

Although it is generally recommended to limit the intake of dietary fat to maintain proper body weight, there are lipid-based components that can contribute to weight control, such as conjugated linoleic acid (CLA), modified glycerides, and fish oil.

Conjugated linoleic acid. One bioactive food component that has drawn significant attention for its antiobesity effect is CLA. It was originally found as an anticancer component from ground beef extract in 1985 (Pariza & Hargraves 1985). Since then a number of other biologically

beneficial effects of CLA have been identified, including antiatherosclerosis, immune-modulation, antidiabetes, antiosteoporosis, and antiobesity effects (Park 2009, Park & Pariza 2007, Park & Pariza 2009).

The name CLA was given based on the fact that CLA is a mixture of geometric and positional isomers of linoleic acid. There are a number of CLA isomers reported. However, because of their biological functions, two main isomers are the focus of current research: *cis*-9, *trans*-11 and *trans*-10, *cis*-12 (Pariza 2004, Park & Pariza 2007). The *cis*-9, *trans*-11 isomer is the predominant isomer found in natural sources, such as beef, milk, and dairy products (Park 2009). The origins of this isomer are either from biohydrogenation of linoleic acid to stearic acid by rumen bacteria or from the delta-9 desaturation of *trans*-11 vaccenic acid in mammalian tissues (Park 2009). The other major isomer of CLA, *trans*-10, *cis*-12, is present at very low levels in food but primarily originates from synthetically prepared CLA (Park & Pariza 2007). Currently most studies on the bioactivities of CLA have used these two mixed isomers. It is known that the effects of CLA are the result of interaction between these two isomers (Pariza 2004, Park 2009).

It is well recognized that CLA, particularly the *trans*-10, *cis*-12 isomer, reduces body fat in animal models while improving lean mass and bone mass (Park et al. 1997, Park et al. 1999). Multiple mechanisms have been suggested for CLA's effect on body fat reduction: (*a*) increasing energy expenditure by enhancing thermogenesis and enhancing UCP expressions, (*b*) modulating lipid metabolism by decreasing lipogenesis and increasing lipolysis, (*c*) reducing adipocyte cell number and size by increasing apoptosis and inhibiting lipoprotein lipase from adipocytes, and (*d*) increasing fatty acid β-oxidation in skeletal muscle (Kennedy et al. 2010, Park & Pariza 2007). It has been suggested that CLA's effects on adipocytes are mediated by interaction with PPAR γ, NF-κB, AMPK, tumor necrosis factor-α (TNF-α), and/or inflammatory mediators (Jiang et al. 2009, Kennedy et al. 2010). However, at the moment it is unknown whether CLA has potential upstream targets for its activities on adipocytes.

The efficacy of CLA in human studies on body fat control was much less significant than that seen in animals (Park 2009). This is suggested to be due to: (*a*) lower doses used in human compared to animal studies, (*b*) differences in age, gender, duration used, and CLA preparations, and most importantly (*c*) differences in experimental design. Regarding the latter, animals were not restricted with regard to energy, whereas most human studies were restricted with regard to calorie intake (Park 2009, Park et al. 1999).

The main health concerns for CLA consumption are lipodystrophy, fatty liver, glucose intolerance, and increased oxidative stress (Pariza 2004, Park 2009, Park & Pariza 2007). Lipodystrophy, fatty liver, and glucose intolerance are mainly associated with animal models, whereas minimal effects were observed in human studies [for review of animal and human studies, see Park (2009)]. Increased oxidative stress by CLA supplementation has been reported in human studies, although the significance of this observation still needs further evaluation.

Modified glycerides. The majority of naturally occurring fats and oils are in the form of triacylglycerols (TAG), with minor components as forms of diacylglycerols (DAG) and monoacylglycerols (MAG). There was great interest on the effects of DAG in recent years as a tool to control obesity [for review, see Hibi et al. (2009) and Rudkowska et al. (2005)]. The suggested mechanism of DAG is mainly attributed to its unique structural and metabolic characteristics, rather than differences in fatty acid composition, digestibility, and energy values compared with DAG and TAG (38.9 kJ g^{-1} and 39.6 kJ g^{-1}, respectively) (Murase et al. 2001, Rudkowska et al. 2005). It is suggested that instead of 2-monoacylglycerol and free fatty acids, the digested products from TAG, the end products of DAG digestion are glycerol and free fatty acids, which may be less

likely incorporated into chylomicrons (Tada 2004, Yang & Kuksis 1991). Thus, free fatty acids from digested DAG are moved into the liver directly.

DAG consumption is also associated with modulating blood lipid profiles, particularly triglyceride and cholesterol, and improving glucose metabolism (Saito et al. 2006, Takase et al. 2005, Yanai et al. 2008). Consumption of DAG also has been associated with increased fatty acid β-oxidation in the liver. It is suggested to be associated with influx of free fatty acids to the liver (Hibi et al. 2008, Jackman et al. 2006, Meng et al. 2004, Osaki et al. 2008).

The overall effects of DAG in weight loss or body fat are rather inconsistent. Some reported reduced body weight (Maki et al. 2002, Nagao et al. 2000), whereas others reported no changes in weight with DAG (Teramoto et al. 2004, Yamamoto et al. 2001, Yasunaga et al. 2004). DAG consumption is associated with increased energy expenditure as the major beneficial effect (Kawashima et al. 2008, Maki et al. 2002, Nagao et al. 2000, Saito et al. 2006). Increased energy expenditure mediated by DAG was suggested to be associated with increased resting metabolic rate (RMR), which may be due to diet-induced thermogenesis originating from the differences in metabolism between DAG and TAG (Hibi et al. 2008, Rudkowska et al. 2005). However, others reported no changes of energy expenditure in humans (Hibi et al. 2008, Kamphuis et al. 2003). Maki et al. (2002) suggested that the effects of DAG may not be substantial but could result in cumulative effects over time.

Overall, no adverse effects were reported from animals (Kasamatsu et al. 2005, Soni et al. 2001) or humans consuming DAG for up to one year [for review, see Morita & Soni (2009)].

Fish oils. In addition to its well-known effects of protection against cardiovascular diseases, consumption of long-chain ω-3 fatty acids, such as marine-originated fish oils, has been reported to be associated with obesity prevention (Al-Hasani & Joost 2005, Buckley & Howe 2009, Carpentier et al. 2006, Hill et al. 2007, Parra et al. 2008, Watts et al. 2006). A number of animal studies indicated that fish oil consumption lowered accumulation of adipose tissue mass, particularly in diet-induced obesity models (Buckley & Howe 2009). Human studies, however, were less consistent; beneficial effects were observed in some studies but not in others (Buckley & Howe 2009).

Reported antiobesity mechanisms of fish oil include increasing resting energy expenditure, increasing fat oxidation, and suppressing appetite, as suggested from human studies (Buckley & Howe 2009, Micallef et al. 2009, Perez-Matute et al. 2007). Additionally, feeding ω-3 fatty acids increased expression of genes and protein involved in fatty acid oxidation in liver, intestine, heart, and skeletal muscle, and decreased expression of genes involved in lipogenesis in adipose tissue from animal studies (Buckley & Howe 2009). These are supported by observations of increased skeletal and heart muscle CPT-1, increased skeletal muscle UPC-3, increased skeletal muscle, liver, and heart peroxisomal acyl-CoA oxidase (Acyl-CoA), and increased intestinal lipid oxidation in animal models, all of which can support increased resting energy expenditure and less effective fat oxidation by ω-3 fatty acids (Buckley & Howe 2009).

Potential concerns over fish or fish oil consumption include adverse responses in platelet function, as well as methylmercury and other environmental contaminants, particularly with fish consumption. However, its potential adverse effects must be weighed against the potential benefits, including cardiovascular disease prevention and brain development (Lien 2009, Oken & Bellinger 2008).

Others: Calcium

The consumption of calcium, particularly dairy calcium, has been linked to reduced body weight and/or body fat mass (Astrup et al. 2010, Van Loan 2009, Zemel et al. 2005). There are three

suggested mechanisms associated with calcium and body fat control. First, high intake of dairy calcium increases fecal fat and energy excretion (Astrup et al. 2010, Van Loan 2009). This is due to the formation of insoluble calcium-fatty acid soaps as well as binding to bile acids, thus resulting in a decreased total energy uptake (Astrup et al. 2010). Recently, Christensen et al. (2009) reported metaanalysis of calcium studies, concluding that dairy calcium intake is significantly associated with increased fecal fat excretion. This difference is not dramatic but would result in an estimated 1–2.2 kg weight loss over a one-year period.

Secondly, calcium may modulate lipid metabolism in adipocytes by decreasing de novo lipogenesis and increasing lipolysis (Astrup et al. 2010, Zemel & Sun 2008). This effect has been suggested to be linked to circulating calcitrol, which controls intracellular calcium in adipocytes, resulting in stimulation of lipogenesis and lipolysis as well as suppressing UCP-2 (Zemel & Miller 2004, Zemel & Sun 2008). During a high-calcium diet, calcitrol is suppressed, thus controlling adiposity (Zemel & Miller 2004, Zemel & Sun 2008). Lastly, limited study reported an association between supplementation of calcium and appetite regulation, although this is inconclusive (Astrup et al. 2010).

CONCLUSION

The past decade has laid groundwork to understanding physiological and molecular mechanisms of central and peripheral control of energy balance and adipose biology. This will allow us to perform an efficient search for antiobesity bioactive food components that could specifically regulate central and/or peripheral cellular pathways for the control of food intake, thermogenesis, and adipose development and function. Recently, many exciting findings identified a number of food components with antiobesity properties. The examples presented in this review have highlighted the potential use of some food components in dietary prevention of obesity through targeting various cellular pathways. However, more studies are needed to elucidate the molecular basis underlying the antiobesity properties of these components. Furthermore, studies in improving bioavailability, safety, interaction with food matrix, and effective delivery of these components to the target tissues should also be addressed in order to be used as active food ingredients for the benefit of body-weight control.

SUMMARY POINTS

1. The CNS receives endocrine and nervous signals from adipose tissue, intestine, and other peripheral tissues to control the energy balance between food intake and energy expenditure.
2. Improvement of UCP-regulated thermogenesis and fatty acid oxidation in peripheral tissues contributes to positive energy expenditure and lowering the risk of the development of obesity.
3. Adipose tissue–secreted hormones participate in many aspects of energy balance, such as food intake, systemic energy metabolism, and thermogenesis. In addition, a transcriptional program of adipocyte hyperplasia is likely to be a promising target of dietary prevention of the development of obesity.
4. Energy intake, appetite, and satiety are likely to be targeted by some antiobesity food components (e.g., dietary fiber, berries, capsaicin, citrus extracts, and fish oils).

5. The potential antiobesity functions of soybean, tea, capsaicin, some spices (curcumin, black pepper, ginger, and mustard), CLA, and modified glycerides are largely mediated through stimulation of energy expenditure (e.g., thermogenesis and fatty acid oxidation).
6. Soybean components, curcumin, citrus extract, CLA, modified glycerides, fish oil, and calcium exert their potential antiobesity function through modulation of adipose biology (e.g., adipogenesis and lipolysis) and lipid metabolism in nutrient-sensing tissues such as liver, adipocytes, and intestine.

FUTURE ISSUES

1. In most cases, the in vivo relevance of the antiobesity functions of the food components described above still needs to be demonstrated.
2. It remains to be investigated whether there are any food components that could cross the blood-brain barrier for direct control of central food intake.
3. Dietary regulation of lipid and energy metabolism in the intestine remains unclear. Further study is required to resolve this.
4. Improving the stability and solubility of antiobesity food components in the gastrointestinal tract will provide great value to increase their beneficial effects on overall energy balance in vivo.

DISCLOSURE STATEMENT

Yeonhwa Park is one of the inventors of CLA use patents that are assigned to the Wisconsin Alumni Research Foundation.

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Errata

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