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MECHANISTIC EFFECT OF DIETARY COMPONENTS IN MANAGING OBESITY

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ABSTRACT

Life style related diseases like obesity, diabetes and cancer threaten the health worldwide. Attention has been focused recently on the study of relation between the food/plant derived components and their effect on target gene to identify the novel pathway involved in the disorder and their future use as therapeutics. Obesity is a complex multifactorial disorder associated with many health problems including hyperlipidemia, hypertension, type2 diabetes, coronary heart disease and cancer. Obesity is caused by the imbalance between the calories intake and the expenditure that lead to the pathological growth and deposition of adipocytes. Adipocytes play a central role in regulating the adipose mass. In obesity, the increased mass of adipose tissue leads to the adipose tissue hyperplasia, triggering the transformation of preadipocytes to adipocytes. The programmed differentiation of preadipocytes to adipocytes is accompanied by increase in the expression of various transcription factors and adipocyte specific-gene. This review highlights on the studies to explain the mechanism of action of various dietary components interacting with proteins involved in adipogenesis.

KEYWORDS: Obesity occurs as a result of genetic and acquired.

INTRODUCTION

Obesity occurs as a result of genetic and acquired changes in biochemical processes which are understood at the molecular level.[1]

Feeding control, which determines the sensation of satiety and hunger through processes of interplay between internal signals like leptin and environmental factors. Leptin regulates food intake by central action inducing expression of SOCS-3 (Suppressor of cytokine signalling),

mRNA in the hypothalamus and stimulates fatty acid oxidation in adipose tissue, (i) by reduction in sterol regulatory element binding protein-1 (SREBP-1), an insulin – stimulated lipogenic transcription factor. (ii) by upregulation of carnitine palmitoyl transferase1 (CPT-acyl CoA oxidase (ACO), peroxisome proliferator activated receptor (PPARα), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), uncoupling protein (UCP-1, UCP-2 and UCP-3) in white adipose tissue (WAT) and liver, causing fatty acid oxidation and disappearance of fat store within adipocytes and liver. However, leptin resistance is a feature of obese humans. Excessive SOCS-3 activity in leptin responsive cells is a potential mechanism of leptin resistance. Protein tyrosine phosphatase PTP1B regulates leptin signalling pathway by targeting the janus kinase (Jak2) protein molecule, a characteristic feature of human obesity. Therefore, PTP1B may be a novel target to treat leptin resistance in obesity.

Energy efficiency, particularly activation of UCP-1, UCP-2 and UCP-3, convert calories contained in food as heat instead of accumulating them as fat.

Adipogenesis, controlled by interplay of transcription factors including PPARα, PPARγ and C/EBP (CCAAT-enhancer binding protein) families.

The knowledge of a growing number of genes and molecules implicated in these 3 types of processes and of their metabolic relationship provides a molecular level understanding of body.

Anti-obesity drugs

Major obesity treatment drugs currently available in the market are - one reduces intestinal fat absorption through inhibition of pancreatic lipase and the other is an anorectic or appetite suppressant. Both types of drugs have side-effects, including increased blood pressure, dry mouth, constipation, headache, and insomnia. A number of anti-obesity drugs are currently undergoing clinical development, including centrally-acting drugs (e.g. radafaxine and oleoyl-estrone), drugs targeting peripheral episodic satiety signals (e.g. rimonabant and APD356), drugs blocking fat absorption (e.g. cetilistat and AOD9604) and human growth hormone fragments. Because of potentially hazardous side-effects, the potential of natural products for treating obesity is under exploration, and this leads as an alternative strategy for developing future effective and safe antiobesity drugs. A variety of natural products, including crude extracts and isolated compounds from plants, can induce body weight

reduction and prevent diet-induced obesity. The valuable medicinal properties of different natural products are due to presence of several constituents i.e. saponins, tannins, alkaloids, alkenyl phenols, glycol-alkaloids, flavonoids, sesquiterpenes lactones, terpenoids and phorbol esters. Among them some act as synergistic and enhance the bioactivity of other compounds.

Anti-obese dietary components

How dietary food components can modify gene expression or transcriptional gene silencing is the subject of nutrigenomics and epigenetics. Among treatments for obesity, one of the most promising strategies in the effort to reduce energy intake through gastrointestinal mechanisms, without altering the central mechanisms, is the development of nutrient digestion and absorption inhibitors. Polyphenols (e.g. L-epicatechin, ECG, EGG, and EGCG), isolated from tea leaves is reported to exhibit strong inhibitory activity against pancreatic lipase. The galloyl moieties within their chemical structures and/or polymerization of their flavan-3-ols bind to and bring the inhibition of pancreatic lipase.[2]

Natural (-)-hydroxycitric acid (HCA) extracted from Garcinia cambogia, acts as a potential natural appetite suppressant. Currently, it is commercial available under the names HCA-SX and Super CitriMax™. This phytochemical act by increasing the release of 5-hydroxytryptamine and serotonin which are implicated in the regulation of eating behavior and appetite control.[3]

Citrus aurantium flavonoids (CAF) were studied on the inhibition of adipogenesis and adipocyte differentiation in 3T3-L1 cells. CAF suppressed adipogenesis in 3T3-L1 adipocytes. Results indicated that CAF down-regulates the expression of C/EBPb and subsequently inhibits the activation of PPARγ and C/EBPα. The anti-adipogenic activity of CAF was mediated by the inhibition of Akt activation and GSK3b phosphorylation. This induced the down-regulation of lipid accumulation and lipid metabolizing genes, inhibiting adipocyte differentiation.[4] The effect of dietary fatty acids on gene regulation via transcription factors was studied in mice by Sanderson and group.[5] They concluded that the effects of dietary unsaturated fatty acids on hepatic gene expression are almost entirely mediated by PPARα and mimic those of synthetic PPARα agonists in terms of regulation of target genes and molecular mechanism.

The spices fenugreek, garlic, ginger, onion, red pepper and turmeric are known to be effective as hypocholesterolemics under conditions of experimentally induced hypercholesterolemia

and hyperlipidemia. Fenugreek is effective in diabetes, where as garlic and onions are effective in humans with induced lipemia. Curcumin, capsaicin and garlic lowered the cholesterol which was observed by its ability to reverse the deformity and fragility of erythrocytes.[6] Fenugreek (*Trigonella foenum-graecum*) seeds, used as a condiment, are documented for health benefits including amelioration of abnormalities in lipid homeostasis due to its hypolipidemic properties. Hypocholesterolemic effect of germinated fenugreek seeds in human subjects (12.0 and 18.0 g) was studied. Subjects fed with 18.0 g of germinated fenugreek powder showed decreased total cholesterol and LDL levels.[7] In another study headed by Bhat,[8] the hypolipidemic effect of thermostable extract of fenugreek seeds (TEFS) was evaluated *in vitro* by employing differentiating and differentiated 3T3-L1 cells, and HepG2 cells cultured in normal or sterol-enriched conditions. At molecular level, TEFS inhibited accumulation of fat in differentiating and differentiated 3T3-L1 cells via decreased expression of adipogenic factors such as peroxisome proliferator activated-receptor-γ (PPAR-γ), sterol regulatory element-binding protein-1 (SREBP-1), and CAAT element-binding proteins-α (c/EBP-α). They also showed that following TEFS treatment, cellular triglycerides (TGs), and cholesterol concentrations decreased significantly ($P < 0.05$) in HepG2 cells via reduced expression of SREBP-1, at mRNA as well as protein level. Under sterol enriched condition, TEFS upregulated low-density lipoprotein receptor (LDLR) expression resulting in enhanced LDL uptake. Treating fat supplement fed C57BL6/J mice with TEFS for 15 days resulted in decrease of serum TG, LDL-cholesterol (LDLc), and body weight in a dose- and time-dependent manner ($P < 0.05$). Results indicated that the hypolipidemic effect of TEFS is due to inhibition of fat accumulation and upregulation of LDLR.[8] Diosgenin, a major aglycone of saponin in fenugreek promotes adipocyte differentiation and and inhibits the expression of several molecular candidates associated with inflammation in 3T3-L1 cell.[9]

The positional changes in the fatty acids in blended oil was introduced using lipase-catalyzed interesterification which could differentially modulate circulating LDL levels in rats compared with those observed in rats given a physical blend of oils. The molecular basis of these differences, transcriptional profiling of genes involved in cholesterol homeostasis was studied after feeding rats with a semipurified diet containing 10% fat from native oils; coconut oil (CNO), rice bran oil (RBO), or sesame oil (SESO); blended (B); CNO+RBO(B) or CNO+SESO(B) and interesterified oil (I); CNO+RBO(I) or CNO+SESO(I) for 60 d. Hepatic LDL receptor (LDL-R) expression significantly increased in rats fed interesterified

oils by 100–200% compared with rats fed blended oils and by 400–500% compared with rats fed CNO. Positional alteration in fatty acids of oils used in the diet induced changes in LDL-R expression, which was accompanied by parallel changes in cholesterol-7a-hydroxylase (CYP7A1) and SREBP-2 genes. This suggested that not only the fatty acid type but also its position in the TG of dietary lipids play an important role in maintaining plasma cholesterol levels by suitably modulating gene expression for LDL-R in rat liver.[10]

Parra and group[11] aimed to find the role of miRNAs expression influenced by conjugated linoleic acid (CLA), which is currently used to induce fat loss. Retroperitoneal adipose tissue (rWAT) expression of five miRNAs related to adipocyte differentiation (miRNA-143), lipid metabolism (miRNA-103 and -107) and altered in obesity (miRNA-221 and -222) was determined. Results indicated the expression of selected miRNAs was modified in response to CLA treatment and metabolic status. Interestingly, a strong correlation was observed between miR- 103 and -107 expression, as well as miR-221 and -222. Moreover, changes in miRNAs expression correlated with several adipocyte gene expressions: miR-103 and -107 correlated with genes involved in fatty acid metabolism whereas miR-221 and miR-222 correlated with the expression of adipocytokines. These findings provide the evidence that miRNAs expression is influenced by dietary manipulation, reflecting the new metabolic state originated by CLA treatment. The same group [12] showed decreased body weight and fat accretion modulated by CLA with the involvement of gut microbiota in mice. CLA supplementation was associated with an increase in stomach protein expression, and exerted a prebiotic action on *Bacteroidetes/Prevotella* and *Akkermansia muciniphila*. However, CLA supplementation was not able to override the negative effects of HF diet on *Bifidobacterium* spp., which was decreased in both High fat (HF) and HF+CLA groups. These data show that CLA are able to modulate stomach protein expression and exert a prebiotic effect on specific gut bacterial species.[12] The gum resin of the tree *Commiphora mukul*, has been used in Ayurvedic medicine to treat a variety of ailments. The active compounds in this resin are the *cis* and *trans* isomers of guggulsterone (GS) (4,17(20)-pregnadiene-3,16-dione). The effect of guggulsterone (GS), on apoptosis, adipogenesis, and lipolysis using 3T3-L1 cells was studied by Yang et al.[13] Their results indicated that in mature adipocytes *cis*-GS decreased viability, whereas the *trans*-GS isomer had little effect. *cis*- and *trans*-GS increased caspase-3 activity and release of cytochrome *c* from mitochondria. The adipocyte-specific transcription factors PPARγ2, C/EBPα, and C/EBPβ were downregulated after treatment with *cis*-GS during the maturation period. Furthermore,

cis-GS increased basal lipolysis of mature adipocytes, but *trans*-GS had no effect. These results indicated that the GS isomers exert antiobesity effects by inhibiting differentiation of preadipocytes and by inducing apoptosis and promoting lipolysis of mature adipocytes. The *cis*-GS isomer was more potent than the *trans*-GS isomer in inducing apoptosis and lipolysis in mature adipocytes.[13] Same group has shown the apoptotic effect of ajoene on 3T3L1 adipocytes. Ajoene is a garlic-derived compound and has a greater chemical stability than allicin. Ajoene treatment resulted in activation of JNK and ERK, translocation of apoptosis inducing factor (AIF) from mitochondria to nucleus, and cleavage of 116-kDa PARP-1 in a caspase-independent manner. Ajoene treatment also induced an increase in intracellular ROS level. Furthermore, the antioxidant *N*-acetyl-L-cysteine effectively blocked ajoene-mediated ROS generation, activation of JNK and ERK, translocation of AIF, and degradation of PARP-1. These results indicate that ajoene-induced apoptosis in 3T3-L1 adipocytes is initiated by the generation of hydrogen peroxide, which leads to activation of mitogen activated protein kinases, degradation of PARP-1, translocation of AIF, and fragmentation of DNA. Ajoene thus influence the regulation of fat cell number through the induction of apoptosis.[14]

Genistein, an isoflavone, was shown to have therapeutic effects for obesity, diabetes and cardiovascular diseases. The effect and underlying mechanism of genistein on adipogenesis in 3T3-L1 preadipocytes was studied. Genistein abolished the phosphorylation of janus-activated kinase 2 (JAK2) in response to MDI. AG490, a JAK2 inhibitor, suppressed the expression of CCAAT/enhancer binding protein alpha (C/EBPα), a marker of adipocyte differentiation. The findings suggest that genistein attenuates the differentiation of 3T3-L1 involving multiple signal pathways.[15]

Hwang and group[16] studied the effects of genistein, EGCG, and capsaicin on adipocyte differentiation in relation to AMPK activation in 3T3-L1 cells. Genistein (20–200 μM) significantly inhibited the process of adipocyte differentiation and led to apoptosis of mature adipocytes. Genistein, EGCG, and capsaicin stimulated the intracellular ROS release, which activated AMPK rapidly. The results suggested that AMPK is a novel and critical component of both inhibition of adipocyte differentiation and apoptosis of mature adipocytes by genistein or EGCG or capsaicin further implying AMPK as a prime target of obesity control.[16]

Tempol, is a low molecular weight antioxidant. Tempol in the food of mice prevents obesity causing significant weight loss without toxicity. Tempol inhibited differentiation of 3T3-L1 cells resulting in a reduction in cellular lipid storage, down-regulation of protein levels of key adipogenesis transcription factors (PPAR-γ and PPAR-α), down regulation of prolyl hydroxylase, and up-regulation of HIF-1α. Mice on a Tempol diet demonstrated reduced systemic levels of IGF-1, in qualitative agreement with that observed in vitro in 3T3-L1 cells, which also show lower IGF-1 levels as a result of Tempol treatment. These results show that treatment of 3T3-L1 cells with Tempol inhibits the expression of key adipogenesis factors, adipose differentiation, and lipid storage has effects on body weight in vivo.[17]

SUMMARY

Obesity is the interplay of genetic, hormonal and lifestyle imbalance leading to the variation in the expression of various proteins. The dietary ingredients affect the molecular targets by down regulating the effectors of adipogenesis, thus culminating the process. As these components are food derived, they are less or non toxic and could be consumed safely. The dosage of consumption of dietary factors has to be determined to envisage the outcome in humans.

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