S3 - 3

Current Status and Prospect of Antiobesity Functional Agents

Myoung-Sool Do

School of Life and Food Sciences, Handong Global University, Pohang, Gyeongbuk 791-708, Korea
E-mail: msdo@handong.edu

ABSTRACT

The obese population has been increasing over the world wide and obesity became a socioeconomic problems. It is become more serious by the accumulation of the knowledge that the obesity is related directly or indirectly with several diseases like, diabetes, hypertension, etc. With these reasons, many functional food or agents for the purpose of weight loss have been developed. However, most of these remedies are unproven and some have produced even dangerous side effects due to the ephedrine alkaloids contained in Ma-Hang. Because of these reasons, they banned using of these agents in US and regards the antiobesity functional agents as drugs in Europe. Several functional agents are known for weight loss activities like, HCA, L-canitine, CLA, chitosan, calcium supplements and capsaicin containing red pepper, *kimchi* and *kochujang*. We describe here about the function, efficacy and mechanism of these antiobesity functional agents. Furthermore, the trial of the mixture of weight loss related herbal ingredients for safe multifunctional antiobesity functional agents are discussed here, as well.

INTRODUCTION

The problem of obesity

Obesity can be defined as a disease in which excess body fat has accumulated such that health may be adversely affected. International obesity task force (IOTF) has recently reported that 1.7 billion people, 1/4 of the whole world population, need to reduce their weight and around 312 million people are overweight by more than 13.5 kg. According to the statistics of the US government, 2/3 of the whole US population are overweight or obese and 31% of the US population is classified as obese. Obesity is increasing in Korean population, as well. Korean Society of Study of Obesity (KSSO) has strengthened the criteria of obesity as BMI value of >25 from >30. The reason for the strengthening of the criteria for obesity as >25 is that oriental people has less muscle compared to the western people even with the same weight and this makes oriental people prone to diabetes and cardiovascular diseases. This strengthened criteria makes 1/3 of the whole Korean population as obese. Obesity causes many health problems. Obesity is associated with the development of type 2 diabetes mellitus, coronary heart disease (CHD), an increased incidence of certain forms of cancer, respiratory complications and osteoarthritis of large and small joints. In the Farmington Heart Study, the risk of death within 26 years is increased by 1% for each extra pound (0.45 kg) increase in weight between the ages of 30 years and 42 years, and by 2% between the ages of 50 years and 62 years (1). These data proves that 4~5% of weight loss will help to decrease the obesity-related diseases. For these reasons there is a big effort to develop antiobesity drugs, it is known that more than 100 therapeutics are under development in US alone. If the developing cost for one therapeutic drug counts for 802 million dollars (Drug development center, Tufts Univ.), then the market for antiobesity drug will have huge potential.

The mechanism of body weight control and therapeutic drugs for obesity

The weight controlling mechanism can be divided into 4 parts in our body. The first one is the afferent signal which is made from the adipocytes and sent to the brain, and the second one is the hypothalamus which reacts to this signal, the third is the afferent signal which links appetite and energy expenditure according to the signal from the brain, and the last one is the adipocytes where energy is absorbed and stored (2). Simply, controlling of appetite, energy expenditure and stored fat would be the weight controlling mechanism in our body. These parts are linked together and cannot function alone, and therefore, energy absorption and energy expenditure can be controlled in homeostasis. Therefore, the drug for obesity should be a substance that can affect all these different parts.

There are two therapeutic drugs for obesity at the moment, Sibutramine (Reductil, Meridia) and Orlistat (Xenical). Sibutramine suppresses the reuptake of noradrenaline and serotonine (5-HT) which is secreted in post-symaptic cleft, and increases the concentration of these molecules in hypothalamus (3). Sibutramine accelerates thermogenesis as well as the suppression of appetite (4). Orlistat (Xenical), a inhibitor of lipid absorption, blocks the pancreatic lipase and suppresses the absorption of lipid. Normally, the greatest effect can be reached when the food obtained contains at least 30% of lipid (5). The known side-effects are occurrence of GI disorder, steato-rrhea, and fecal urgency. Although this may reduce fat soluble vitamine absorption, no significant problem has come to attention during the 2 years of clinical studies (6). One of the most effective weight loss drugs was fenfluramine, known as fen-phen, but it was pulled from the market in 1977 after it was found to be linked to potentially fatal heart problems. These events paved way for introduction of safe and less problematic special functional agent for the treatment of obesity.

ANTIOBESITY FUNCTIONAL AGENTS

As mentioned above, the functional agents for obesity should contribute to a lower intake, a higher energy expenditure and a decrease in the formation of adipocytes. The search for weight controlling food began in the mid-19th century when industrialization led to widespread obesity. At that time, people have tried to lose weight by avoiding particular food groups and eating specific foods such as cabbage soup, or adding a certain ingredient, like vinegar or grapefruit to each meal. In 1994, the Dietary Supplement Health and Education Act eliminated the need for manufacturers to prove the efficacy of the ingredients used in over-the-counter weight loss products. And this has led to a wide array of food extracts and herbal ingredients sold in health food stores. Most of these remedies are unproven and some have produced dangerous side effects. These are products containing ephedrine alkaloids derived from Ephedra sinica also known as Ma huang or Chinese ephedra, Due to the number of adverse events, including several deaths, reported in individuals taking products containing ephedra alkaloids, the Food and Drug Administration banned all such supplements in the United States in February 2004 (FDA, 2004). In all EU countries in 2005 vitamins and other dietary supplements are treated as though they are drugs. Because of these reasons, there are not many commercially used functional agents for antiobesity effects. Here we describe about the function and the mechanisms of these functional agents, such as hydroxycitric acid (HCA), L-carnitine, conjugated linoleic acid (CLA), chitosan, dairy calcium and associated protein, green tea (catechin), *kochujang* and *kimchi*.

Hydroxycitric acid (HCA)

(-)-Hydroxycitric acid (HCA) is an active ingredient extracted from the rind of the Indian fruit *Garcinia cambogia*. The dried and cured pericarp of the fruit of this species contains up to 30% by weight of hydroxy-

citric acid (HCA) (7). (-)-Hydroxycitric acid (HCA) is a competitive inhibitor of adenosine triphosphate citrate lyase (8), which catalyzes the extramitochondrial cleavage of citrate to oxaloacetate and acetyl coenzyme A. This action of HCA should reduce the acetyl coenzyme A pool, thus limiting the availability of 2-carbon units required for fatty acid and cholesterol biosynthesis (8). A second possible mechanism for an anorectic effect of HCA is that by reducing acetyl CoA, malonyl CoA levels are depressed thereby reducing negative feedback on carnitine acyltransferase. This leads to increased lipid transport into the mitochondria and inefficient oxidation with resultant ketone body formation. Ketones are purported appetite suppressants, however, several groups have failed to observe an association between ketosis and reported hunger level (9). In animal study, it has been demonstrated that the combination of HCA supplementation and swimming treatment for 8 weeks reduced body weight and body fat in high-fat diet fed male Sprague-Dawley rats (10).

L-Carnitine

L-Carnitine is a naturally occurring substance required for energy metabolism in mammals. It is produced by the body and is also available in the diet mainly in products of animal origin. L-Carnitine is essential for the transport of long chain fatty acids across the mitochondrial membrane for subsequent fat degradation and energy production. Another important function of L-carnitine is the ability to shuttle short chain fatty acids from inside the mitochondria to the cytosol. Therefore, L-carnitine is responsible for maintaining energy metabolism of the whole body. The rationale for carnitine supplementation as a weight-loss agent is based on the assumption that regular oral ingestion of the substance increases its intracellular concentration. This would trigger increased fat oxidation and gradual reduction of the body's fat reserves. Several studies have shown that oral carnitine ingestion (up to 6 g/d for 14 d) does not change muscle carnitine concentration in healthy non-obese humans and does not promote weight loss (11). Recent data have indicated that high doses of L-carnitine modulate glucocorticoid receptor function and, hence, might mimic some of the biological activities of glucocorticoids, which are known to stimulate lipolysis in adipose tissue (12).

Conjugated linoleic acid (CLA)

CLA is found in dairy products, lamb, veal calves, cattle, seafood, turkey and vegetable oils (13). LA is changed into CLA by bihydrogenation of fermentation bacteria, *Butyrovibrio fibrisolvens* (13). CLA has two isomer forms; *cis*-9, *trans*-11 CLA (c9t11) and *trans*-10, *cis*-12 CLA (t10c12), and the major isomer of CLA in natural foods is c9t11. T10c12 CLA controls lipid metabolism, body fat gain and regulates adipocyte secreted hormones *in vivo* (14) and *in vitro* (15). Trans-10, cis-12 CLA also induces the apoptotic effect in preadipocytes (16). Several studies show CLA decreases adipocyte cellularity by decreasing proliferation (16) or adipocyte size (16). It is also shown that CLA mixture elevated the secretion of TNF-α in rat primary culture (17). In mice, supplementation of CLA reduces weight gain and fat deposition independent of dietary fat levels (18). Although no adverse effects of CLA have been observed in pigs, fat liver and spleen as well as insulin resistance have been reported in mice after CLA supplementation (19). Some human studies showed slight reduction of body fat mass or calculated fat percentage after CLA supplementation, while others failed to show any effect (20). More experiments are needed humans to ascertain the efficacy and investigate mechanisms and safely of specific CLA isomers.

Chitosan

Chitosan, a partially deacetylated polymer of N-acetylglucosamine, derived from a polysaccharide, chitin, appears to bind to negatively charged lipids in animal trials, hence reducing their gastrointestinal uptake (21) and

lowering serum cholesterol (22). Chitosan binds to fatty acids and the binding is mainly of ionic nature: in fact the salt is prepared by neutralization of chitosan with edible fatty acids such as oleic, linoleic, palmitic, stearic and linolenic acids. The resulting salts, after ingestion, bind to additional lipids (triglicerides, fatty and bile acids, cholesterol and other sterols) probably by hydrophobic interactions and a great portion of these bound lipids are excreted rather than absorbed.

Some human trials have suggested that chitosan may decrease body weight and serum lipids (23). In a recent study with 250 overweight and obese adults on a 24 weeks trial, chitosan treatment did not result in a clinically significant loss of body weight compared to placebo (24). Another study shows that dietary chitosan reduces plasma cholesterol probably by the reduction of cholesterol absorption in a 4 weeks feeding study of male Sprague-Dawley rats (25).

Dairy calcium and its associated protein

It has been reported that hiigh calcium, low-calorie diet helped obese mice lose weight at the rates of double than that of mice fed with a low-calcium, low-calorie diet. The effect was even stronger in mice fed with diets containing dairy calcium (26). The reason that dairy calcium was more effective than supplemental calcium carbonate may relate to the amino acid composition of the protein in the dairy calcium supplement. It has been found that women who consumed less than 700 g of calcium a day lost less weight than those who consumed an equal number of calories but 20% more calcium (27). It remains to be seen if the enhanced weight loss observed with dairy calcium is related to dairy proteins, or other agents. It also has to be determined whether a low-calorie, high-calcium diet provides adequate physiological and psychological satiety to achieve long-term weight management. Another factor that the relatively high levels of calcium in these diets may interfere with absorption of other divalent minerals has to be considered.

Green tea and catechin

It has been reported that green tea extract increased thermogenesis by 4% over a 24-h period in healthy male volunteers (28). According to these researchers, the thermogenic properties of green tea may reside primarily in an interaction between its high content of catechin-polyphenols and caffeine on sympathetically released noradrenaline. Catechin-polyphenols are known to be capable of inhibiting catechol-O-methyl-transferase (the enzyme that degrades noradrenaline), and caffeine has been shown to inhibit transcellular phosphodiesterases (enzymes that break down NA-induced cyclic AMP). Therefore, it has been proposed that green tea extract, via its catechin, polyphenol and caffeine content, are effective in stimulating thermogenesis by relieving inhibition at different control points along the NAcAMP axis (27,28).

Capsaicin, red pepper, *kochujang* and *kimchi*

Capsaicin activates the parasympathetic nervous system, which triggers release of catecholamine (29), which then stimulates the β-adrenergic receptor. The energy metabolism triggered by the activation of β-adrenergic receptor results in the decreased body fat mass (30).

Capsicum species, hot pepper, is an important plant and have been used world wide as food, spices, and medicines. Red pepper increased plasma catecholamine levels and induced lipolysis (31) and can reverse the effects of high fat diet on weight and blood and tissue lipids (32). Red pepper and capsaicin, (E)-N-[(4-hydroxy-3-meth-oxyphenyl)methyl]-8-methyl-6-nonenamide, have been reported to increase lipid oxidation in Japanese women (33).

It has been demonstrated that high pungency red pepper extract increased lipolytic activity of rat adipocytes *in vitro*, as well (34). Another study showed that adipocyte proliferation effect was highest in the green pepper and

the placenta which has the highest capsanoid, respectively (35). There were two separate studies about the anti-obesity effects of *kochujang*, a Korean red pepper paste (36,37). These studies suggest that *kochujang* reduces the body weight, lipid levels of adipose tissues and serum in high-fat fed SD rats. The interesting point was that fermented *kochujang* exhibited more suppressive effects on body fat gain and lipid levels of adipose tissues and serum than the *kochujang* whthout fermentation and red pepper alone, indicating that more than red pepper was involved in the antiobesity effect of *kochujang*.

Kimchi is the most favorable food in Korean population. There were several reports that *kimchi* has antiobesity effects. Kwon et al. (38) reports that *kimchi* consumption is beneficial to elevate HDL-C and lower LDL-C level in the middle-aged Korean population. Other report shows that *kimchi* supplementation while practicing exercise might improve the obese state by reducing body fat content as well as reducing plasma lipids (39). In a study with the *kimchi* solvent fraction, dichloromethane (CH_3Cl_2) fraction seems to have the most active components, which decreases accumulation of lipids in heart, kidney, and lung of high cholesterol fed rabbit (40).

PROSPECTS AND CONCLUSION

As mentioned above, if many different factors can cause obesity it is doubtful that a single agent alone will be an effective treatment for all over-weight people. It is more likely that an array of functional agent, affecting different weight management needs, would be an ideal candidate for effective treatment. For these reasons, there has been increasing usage of combination of several functional agent or oriental herb ingredients for weight loss. Kang et al. (41) have studied about the role of the mixture on weight loss related to herbal composition and showed that treatment of high-fat fed SD rat with herbal mixture significantly decreased the weight gained and epididymal fat mass compared to the control group. They also showed that serum cholesterol level was significantly reduced and the ratio of HDL cholesterol and total cholesterol was promoted (41). Another study showed the weight loss effect of a natural composition containing oriental herbs, KSH28 (42). They showed that body fat was significantly reduced without significant side effect compared to baseline value. It also is important to understand the emotional status underlying many people's eating behaviors. To maximize their effectiveness, functional weight loss agents may need to be used in combination with behavioral therapy, as well.

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