Food Components Modulate Obesity and Energy Metabolism via the Transcriptional Regulation of Lipid-Sensing Nuclear Receptors

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Summary  Obesity is a major risk factor for chronic diseases such as diabetes, cardiovascular diseases, and hypertension. Many modern people have a tendency to overeat owing to stress and loosening of self-control. Moreover, energy expenditure varies greatly among individuals. Scientific reduction of obesity is important under these circumstances. Furthermore, recent research on molecular levels has clarified the differentiation of adipocytes, the level of subsequent fat accumulation, and the secretion of the biologically active adipokines by adipocytes. Adipose tissues and obesity have become the most important target for the prevention and treatment of many chronic diseases. We have identified various food-derived compounds modulating nuclear receptors, especially peroxisome proliferators-activated receptor (PPAR), in the regulation of energy metabolism and obesity. In this review, we discuss the PPARs that are most important in obesity and energy metabolism.

Key Words  obesity, food function, nuclear receptors, PPARs

In recent decades, the prevalence of obesity throughout the world has progressively increased. This unabated rise has spawned proportionate increases in obesity-associated metabolic disorders. Genes specific to obesity are expressed sequentially in adipocyte formation. Research on adipogenesis from multipotent mesenchymal stem cells to mature adipocytes is currently being actively pursued. Adipose tissues and obesity have become the most important target for the prevention and treatment of many chronic diseases. In particular, it has been clarified that adipokines secreted by white adipocytes play a significant role in the pathogenesis of diseases such as diabetes and cardiovascular diseases. Furthermore, it is revealed that inflammation in adipose tissue is closely associated with the pathogenesis and exacerbation of diseases arising from obesity and the abnormality of energy metabolism.

Nuclear Receptors, Ligands and Functions  Some members of the nuclear receptor (NR) superfamily are lipid-sensing transcription factors that translate signals from the constantly changing lipid environment into gene expression changes. The superfamily of NRs comprises 48 members that are classified into 6 subfamilies based on sequence alignment and phylogenetic tree construction. Transcriptional activities of some NRs are regulated by small lipophilic ligands, while other NRs are called “orphans,” because their endogenous ligands are unknown.

Certain NRs, especially lipid-sensing NRs including peroxisome proliferator-activated receptor (PPAR), are important in the regulation of whole-body energy metabolism, which makes them attractive targets for drugs and functional food factors for the management of metabolic disorders. Interestingly, natural compounds that act as agonists or antagonists of NRs (Table 1) may be useful for the management of obesity accompanied by lipid metabolism abnormalities. The PPAR subfamily consists of PPARα, PPARγ, and PPARδ (also known as PPARs). These receptors initially became the focus of intense investigation following the discovery that PPARα and PPARγ are the molecular targets of major classes of drugs used to correct abnormalities in lipid and glucose homeostasis. Fibrates are useful for the treatment of hyperlipidemia target PPARα, while thiazolidinediones (TZDs) are effective ligands for PPARγ, and have revolutionized the treatment of insulin resistance. Furthermore, high-affinity PPARδ agonists also have been shown to improve metabolic disorders. Various endogenous fatty acids are low-affinity ligands for PPARs acting as physiological ligands in vivo.

PPARs and Food Components  PPARα was the first PPAR to be identified and was shown to be the target of hypolipidemic fibrate drugs in the liver. PPARα is characterized by a high rate of fatty acid oxidation. It is shown in many reports that PPARα is activated by endogenous long-chain unsaturated fatty acids. Therefore, fatty acids from foods have been of interest as the activators of lipid metabolism, that is, the beneficial effects of polyunsaturated fatty acids on...
normal health and chronic diseases related to obesity (3, 4). Recent studies have shown that both conjugated linoleic acid (CLA) and its derivatives (octo-octadecadienoic acids, oxo-ODAs) modulate PPARα activity. 9-oxo-10,12-ODA and 13-oxo-9,11-ODA from tomato and tomato juice, 13-oxo-9,11-octadecadienoic acid derived from tomato is a potent peroxisome proliferator-activated receptor α agonist to decrease triglyceride accumulation in mouse primary hepatocytes. Mol Nutr Food Res 55: 585–593.

PPARγ serves a master regulator in adipocyte differentiation, lipid storage, and glucose metabolism. Modulators of PPARγ identified in foods have also been abundantly researched. Various flavonoids are associated with anti-inflammatory and antioxidant activities (8). Naringenin, a grapefruit-derived compound, enhances the expression of PPARγ and promotes the regulation of adipogenesis (9). In addition, apigenin, chrysin, and kaempferol have been reported to enhance PPARγ activation (10).

PPARδ is ubiquitously expressed at relatively high levels in the liver, kidneys, cardiac and skeletal muscle, and adipose tissue (11). PPARδ does not appear to be an available drug. However, the availability of potent synthetic high-affinity agonists has been reported. Recently, several natural compounds derived from food that modulate PPARδ activity have been reported. It looks like δ-tocotrienol activates PPARδ in the luciferase assay (12). Administration of tocotrienol-enriched palm oil in mice improves glucose intolerance and enhances PPAR target genes in the muscles. Further, green tea extract (13) and momordin, an extract from bitter melon (14), have also been shown to activate PPARδ.

Prevention of obesity and disorders of energy metabolism due to foods are socially required, and many therapeutic medicines are widely used for these chronic diseases. In this review, we indicate the functionality and availability of PPAR modulators against obesity and energy metabolism from a perspective of food components. In fact, various modulators with unique bioactivities as PPAR ligands that contribute to the regulation of carbohydrate and lipid disorders have been identified in foods. However, exploration of natural modulators is imperative to take advantage of them based on scientific evidence not only in experimental animals but also in human clinical studies.

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| Table 1. Natural modulators of PPARs activity. |
| Compounds | Target receptors | Activity | References |
|------------|-----------------|----------|------------|
| EPA        | PPARα           | activator | 15         |
| DHA        | PPARα           | activator | 16         |
| CLA        | PPARα           | activator | 17         |
| 9-oxo-ODA, | PPARα           | activator | 5, 6       |
| 13-oxo-ODA |                  |          |            |
| phytol     | PPARα           | activator | 18         |
| auraptene  | PPARα, γ        | activator | 19, 20     |
| resveratrol| PPARα, γ, δ     | activator | 21         |
| vaticanol C| PPARα, δ        | activator | 7          |
| (resveratrol tetramer) |          |          |            |
| bixin      | PPARγ           | activator | 22         |
| naringenin | PPARγ           | activator | 23         |
| hesperetin | PPARγ           | activator | 23         |
| apigenin   | PPARγ           | activator | 9          |
| chrysin    | PPARγ           | activator | 9          |
| kaempferol | PPARγ           | activator | 9          |
| genistein  | PPARγ           | activator | 9          |
| β-cryptoxanthine | PPARγ | inhibitor | (under submission) |

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