Food Intake and Thermogenesis in Adipose Tissue

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Brown adipose tissue (BAT) is regarded as a key target for developing interventions to prevent and treat obesity and age-related diseases. In addition, uncoupling protein 1 (UCP1) - expressing “brown-like” adipocytes, known as beige cells, that develop in white adipose tissue (WAT) under certain physiological conditions and pharmacological stimuli. The effects of ageing on BAT atrophy and functional decline further strengthen the notion that healthy eating habits and food choices play an extremely vital role against reduction in the number of BAT and beige cells as people approach middle age. This review aims to cover recent progress in food items and pharmaceuticals that activate or induce BAT and UCP1.

Key words: Food components, Obesity, Brown adipose tissue, Uncoupling protein, Beige cells, Transient receptor potential (TRP) channels

Introduction

Diet-induced thermogenesis (DIT) is defined as an increase in body temperature, which is more than the inducible temperature, due to the metabolism of food consumed during a meal.¹ It has two components: increase in the body heat production due to energy metabolism, by activating the sensory nervous system—the taste and smell of food—and the increase in food digestion and absorption. The former is affected by various factors during food consumption. Recently, “non-energetic food components” such as taste and smell were found to be linked to increase in DIT via sensory nerve stimulation, in addition to the increase due to fat metabolism within brown adipose tissue (BAT). In this review, we will discuss the effect of various factors, along with the food consumption on thermogenesis in adipose tissue.

Adipose tissue and thermogenesis

Obesity is defined as excessive storage of fat by the adipose tissue in the body. It is composed of white and brown adipocytes (Fig. 1).

White adipocytes form white adipose tissue (WAT), which stores energy, whereas BAT is a “heat-producing tissue”, which oxidizes deposited fat and releases the stored energy as heat. Brown adipocytes have many mitochondria, which contain uncoupling protein-1 (UCP1), involved in accelerating heat production by uncoupling ATP synthesis. Heat production is mainly regulated by the sympathetic nervous system. BAT helps to maintain optimum body temperature in a cold environment by generating and dissipating heat from stored energy.

In recent years, it is shown that in healthy ageing humans, reduction of BAT activity might be associated with body fat accumulation in WAT.² These results suggest that, BAT might have a protective role against increase in body fat storage with age. Therefore, BAT is regarded as a key target for developing interventions to prevent and treat obesity and age-related diseases. It is reported that two distinct types of brown adipocytes exist: classical brown adipocytes that arise from muscle-like type progenitors³ and UCP1-expressing “brown-like” adipocytes, known as beige cells, that develop in WAT under certain physiological conditions (such as cold exposure) and pharmacological stimuli (such as beta-adrenergic agonists).^{4,5} Beige

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Fig. 1. White adipocyte and brown adipocyte.

cells also reduce in number as people approach middle age; without these metabolizing cells, fat continues to accumulate for decades called a middle-age spread.^{2,6} Obese WAT exhibited a decrease in energy expenditure.^{7,8} However, there is insufficient understanding of the relationship between the reduction in energy expenditure and the induction of beige cell in WAT from the point of ageing.

BAT atrophy and functional decline

It was elucidated that decreased BAT activity may be associated with accumulation of body fat in WAT with ageing in healthy humans.² It is well known that chronic inflammation leads to metabolic dysfunctions in obese WAT.^{9,10} M1 macrophages (M ϕ) infiltrate WAT via cytokines, mainly monocyte chemoattractant protein-1 (MCP-1), which are released from hypertrophied adipocytes and M1 M ϕ in obese WAT. These infiltrated M ϕ are then activated by free fatty acids from hypertrophied adipocytes, resulting in the secretion of proinflammatory cytokines such as tumor necrosis factor- α (TNF α).^{11,12}

We evaluated that these proinflammatory cytokines—derived from the activated M ϕ —are one of the inhibitory factors involved in the induction of brown-like adipocytes and UCP1 expression that may lead to a decrease in energy expenditure in obese WAT. We further identified TNF α and interleukin-1 beta (IL-1 β) as possible proinflammatory cytokines involved in the suppression of UCP1 expression in adipocytes.^{13–15} These reports suggest a plausible mechanism of UCP1 transcriptional repression in white adipocytes, in

obesity and its related disorder, diabetes. Investigating such a mechanism will provide insights into the physiological and pathological regulation of UCP1 and help develop a solution to overcome the decrease in energy expenditure under obese conditions.

Sensory stimulation by food intake and thermogenesis

Eating not only involves the ingestion of food, but also stimulates the gustatory, olfactory, and somatic senses. Besides the joy, eating also influences other sensory activities. Recently, the signals released in response to sensory stimulation, as well as the physiological phenomena associated with food intake, digestion, absorption, and various hormone secretions were studied.¹⁶ The effect of food components on the nervous and hormonal regulatory system has been largely unrecognized, until now.

However, the significant role of “non-nutrient” food factors in thermogenesis has been established.¹⁷ Le Blanc et al.¹⁸ showed that “palatability” of food acts as a signal affecting the central nervous system, causing catecholaminergic thermogenesis in humans and dogs.

Lipid intake and thermogenesis

Even though the phenomenon of accelerated thermogenesis caused by lipid intake has been observed for a long time, factors affecting this mechanism are poorly understood. In rats, lipid digestion leads to an increase in sympathetic nerve activity causing thermogenesis: it induces a cessation of treatment with cholestyramine, a bile acid sequestrant that blocks the digestion and absorption of lipids and is used to treat hypercholesterolemia. Increase in thermogenesis due to lipid intake is signaled either by the release of fatty acids during lipid digestion or secretion of gastrointestinal hormones in response to these fatty acids.¹⁹

Dietary lipids vary according to their constituent fatty acids, for instance, shortening (containing a high level of saturated fatty acid) and lard (containing a same level of saturated fatty acid and mono-unsaturated fatty acid) affect the concentration of catecholamine in urine due to an effect on sympathetic nerve.^{10,20,21} Interestingly, UCP1 expression also differs with BAT development.^{22,23} Fatty acid receptor, such as G protein-coupled receptors (GPCRs) exist in the

mouth; intraoral recognition of free fatty acids contribute to the depolarization of receptor cells, thereby activating the gastrointestinal organs involved in the digestion and sensing of lipids through the sympathetic nervous system.²⁴ Because the intraoral mechanism of lipid recognition is linked to lipid palatability control^{25,26}, lipid sensory stimulation and the subsequent central phase stimulation are closely associated with the lipid-related thermogenesis.

Recently, we reported that the intake of fish oil containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) enhances energy utilization by inducing UCP1 in both BAT and WAT containing beige cells through transient receptor potential vanilloid 1 (TRPV1) channel-sympathetic nerve system (SNS) and may prevent obesity and its related metabolic disorders.²⁷ Interestingly, we found that a linoleic acid metabolite, produced by gut lactic acid bacteria, enhances energy metabolism by activation of TRPV1 (under submission).

Plant derived compounds and thermogenesis

In 1980s, we studied the effect of spices as a factor in enriching the palatability of food. Pungent ingredients in spices such as pepper induce the acceleration of thermogenesis: “pungent ingredient-in-

duced thermogenesis”.²⁸ These pungent ingredients activate the sympathetic nervous system in the intraoral and digestive tract, resulting in the secretion of adrenaline from the adrenal glands. The adrenergic signal causes the augmentation of energy metabolism and reduction of body fat²⁹⁻³¹, by activating and strengthening of BAT through sympathetic nerve activity.

It is reported that the most effective physiological condition for activating BAT in humans is exposure to cold.^{32,33} This process is postulated to occur through the following mechanism: cold stimulus received by sensory nerves activates the sympathetic nervous system via hypothalamus, which then activates BAT through beta-adrenergic receptors on brown adipocytes. This is considered a type of “central phase stimulus”. Moreover, based on the concept of this process Saito et al. focused on the food component agonist sources of TRPV1, a type of transient receptor potential (TRP) channel. Interestingly, capsinoids, a nonpungent constituent of pepper, and paradol, a constituent of ginger, activate human BAT and increase the expenditure of energy.^{34,35} These results suggest that the continuous stimulation of TRP channel by food components can be a simple and effective means of expression, functional maintenance, and augmentation of BAT via the sympathetic nervous system (Fig. 2). The dietary compounds responsible for BAT and UCP1 activation are

Fig. 2. Schematic summary of anti-obesity effect of food intake via TRPV1 activation.

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; TRPV1, transient receptor potential vanilloid1; SNS, sympathetic nervous system; β-AD, β-adrenergic; UCP1, uncoupling protein 1; BAT, brown adipose tissue; WAT, white adipose tissue.

Table 1. Dietary compounds of activators and inducers on BAT and UCP1

Foods (functional compounds)	Estimated action mechanism
Fatty acids	UCP-1 proton conductance
Vitamin A (all-trans retinoic acid)	UCP-1 proton conductance
Sweetener (sucrose)	sympathetic nervous system
Sweetener (saccharin)	sympathetic nervous system
Mustard (pungency: allyl isothiocyanate)	sympathetic nervous system
Hot pepper (pungency: capsaicin)	TRPV1-sympathetic nervous system
Hot pepper (non-pungency: capsiate)	TRPV1-sympathetic nervous system
Ginger (pungency: paradol)	sympathetic nervous system
Coffee (caffeine)	sympathetic nervous system
Olive (oleuropein)	sympathetic nervous system
Grapefruit (limonene)	sympathetic nervous system
Allonear berry (allonear anthocyanin)	sympathetic nervous system
Brown Seaweeds (carotenoid: fucoxanthin)	unknown
Fish oil (EPA, DHA)	PPARs ligands
	sympathetic nervous system
	UCP1-1 proton conductance?
1-Monoacylglycerol	TRPV1-sympathetic nervous system
Fatty acid derivative (CLA)	PPARs ligands?
	UCP-1 proton conductance?

TRPV, transient receptor potential vanilloid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PPAR, peroxisome proliferator-activated receptor; CLA, conjugated linoleic acid.

summarized in Table 1.

A few other food compounds cause an increase in BAT activity by stimulating adrenaline and noradrenaline secretions, through the interplay between the sympathetic nervous system and adrenal glands. For example, when rats were fed oleuropein, a compound from olive oil, UCP1 expression increased significantly after 28 days; an increase in BAT function, decrease in body weight, and fat pad was also observed.³⁶ Oleuropein, a polyphenolic compound, is abundantly found in extra-virgin olive oil and imparts bitterness. Polyphenols from *Kaempferia parviflora*, a member of the ginger family, enhances UCP1 expression in BAT and decreases fat pad in mouse³⁷ and increases whole-body energy expenditure in humans.³⁸

There are many plant-derived compounds (phytochemicals) such as polyphenols (more than 8000 kinds) and carotenoids (more than 600 kinds) in food. Many epidemiological studies suggest that consumption of polyphenol-rich or carotenoid-rich foods have a beneficial effect on diabetes, obesity, and cardiovascular risk factors. Phytochemicals exert their effect through the antioxidant and anti-inflammatory mechanisms.³⁹⁻⁴² This suggests that phytochemicals in food can act as anti-inflammatory factors, thereby decreasing BAT atrophy and their subsequent functional decline. Further longitudinal studies on human subjects are necessary to confirm the above idea.

Conclusion

Many fatty acids and plant-derived compounds from food activate and strengthen classical brown adipocytes in BAT and beige cells in BAT and WAT through the TRP-induced activation of the sympathetic nervous system via sensory stimulation. The effects of ageing on BAT atrophy and functional decline further strengthen the notion that healthy eating habits and food choices play an extremely vital role against reduction in the number of BAT and beige cells as people approach middle age. In the fight against obesity and metabolic diseases in an ageing society, the generation of food items and development of pharmaceuticals that activate or induce BAT and UCP1 is warranted.

Conflicts of Interest

The authors declare no conflict of interest.

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